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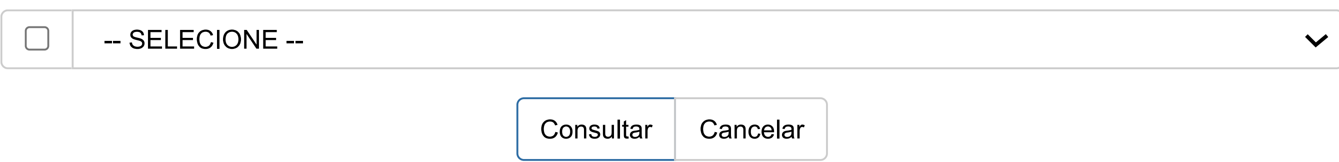

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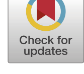

Chloroquine and hydroxychloroquine in antitumor therapies based on autophagy-related mechanisms

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ABSTRACT

Chloroquine (CQ) and hydroxychloroquine (HCQ) are the most common drugs used to relieve acute and chronic inflammatory diseases. In this article, we present a review about the use of CQ and HCQ in antitumor therapies based on autophagy mechanisms. These molecules break/discontinue autophagosome-lysosome fusions in initial phases and enhance antiproliferative action of chemotherapeutics. Their sensitizing effects of chemotherapy when used as an adjuvant option in clinical trials against cancer. However, human related-MDR genes are also under risk to develop chemo or radioresistance because cancer cells have ability to throw 4-aminoquinolines out from digestive vacuoles well. Additionally, they also have antitumor mechanism unrelated to autophagy, including cell death from apoptosis and necroptosis and immunomodulatory/anti-inflammatory properties. However, the link between some anticancer mechanisms, clinical efficacy and pharmacological safety has not yet been fully defined.

1. Introduction

Worldwide, it is estimated 19.3 million new cancer cases and nearly 10 million cancer deaths occurred in 2020 [1]. In particular, the chemoresistance remains the predominant reason of therapeutic failures, as well as adverse side effects [2].

Drug reuse, also called ‘redirection’ or ‘repurposing’, is a new use of known and established compounds for new therapeutic indications. Drug redirection offers the opportunity to identify therapeutics drugs for rare diseases, including some types of cancer. In addition, it saves time and money and improves productivity, in addition to reducing the risks and supplies associated with the development of new drugs. Additionally, the distance between drug discovery and commercial availability is reduced, as previous records allow access to pharmacodynamic, pharmacokinetic, toxicity, drug interaction(s) and clinical databases [3–5].

In addition to malaria, currently, chloroquine [CQ, 4-*N*-(7-chloroquinolin-4-yl)-1-*N*,1-*N*-diethylpentane-1,4-diamine] and hydroxychloroquine [HCQ, 2-(4*S*)-4-(7-chloroquinolin-4-yl)amino]pentylethylamino]ethanol] are the most common drugs used to relieve acute and chronic inflammatory diseases, such as rheumatoid arthritis [6], systemic lupus erythematosus [7,8], Sjogren’s syndrome [8] and sarcoidosis [9]. They are on the World Health Organization’s list of essential medicines as safe and effective medicines needed in a health system [10]. In 2014, HCQ was approved in the treatment of type 2 diabetes in India as a third- or fourth-line medication [11] taking into considerations the beneficial side effects in systemic disorders associated with metabolic syndrome and better control of atherosclerosis, hyperglycemia and hyperlipidemia [12]. In particular, CQ and HCQ have also been widely reported as potential anticancer agents due to their interruption of autophagy [13]. In this article, we present a review about the use of CQ and HCQ in cancer therapy based on autophagy mechanisms.

2. Cellular and molecular anticancer mechanisms

2.1. Autophagy-related mechanisms

Although the exact mechanism of anticancer action of CQ and HCQ is not fully understood, some mechanisms are proposed. Among them, the

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inhibition of autophagy has been the most discussed and accepted.

Autophagy is a well-known evolutionary mechanism of cellular self-degradation in mammalian systems in response to different stimuli/stress, including food deprivation, hyperthermia, hypoxia and xenobiotics. In this context, the catalytic complexes that function as ubiquitin-like conjugation systems play an essential role in elongation the phagophore and recruiting other proteins for the self-digesting process, including vesicular protein sorting 34 (Vps34), beclin-1 and protein kinase p150 (Vps15). These proteins are part of the PI3K class III complex that produces phosphatidylinositol 3-phosphate (PI(3)P) at the phagophore initiation sites [14]. The ATG5/ATG12/ATG16L complex, located at pre-autophagosomal structure (PAS), stimulating the binding of LC3-I to phosphatidylethanolamine (PE) to form lipidized LC3 (LC3-II). Since its initiation in the PAS, the phagophore has elongates into a cup-shaped structure and begins to engulf material, sequestering the material in a double-membrane autophagosome [15,16]. These autophagosomes fuse with lysosomes to produce autolysosomes (also called autophagolysosomes), trigger lysosomal hydrolases and cause the breakdown of internalized substances, producing amino acids, sugars, fatty acids, nucleotides and nucleosides, which return to the cytosol and can re-enter the anabolic cellular circuitries (Fig. 1) [15,17].

Experimental tools have been widely used to assess the cellular aspects resulting from autophagic block. 3-methyladenine (3-MA) inhibits the PI3K class III complex during initial phase of autophagy. Meanwhile, bafilomycin A1, like CQ and HCQ, blocks in the final stage of autophagy, inhibiting the fusion of autophagosome with lysosome [18].

In relation to CQ and HCQ, these compounds containing weakly basic amines which have a strong propensity to become highly concentrated in lysosomes, than lysosomotropic compounds are normally considered to increase the lysosomal pH [19]. As a permeable, non-protonated, basic and weak diprotic molecule at pH 7.4, they can enter cells [20]. Within lysosomes, these compounds acquire a positive charge due to ATPase proton pumps, become trapped and alter the pH of Golgi vesicles and endosomes/lysosomes, reducing their functionality [21]. This interrupts the fusion of the autophagosome with the lysosome, during the formation of autophagic autolysosomes. An additional mechanism considers the involvement of membrane Na^+/H^+ exchangers (NHE) for the uptake of CQ/HCQ together with sodium in the exchange of protons, as shown by specific inhibitors of eukaryotic NHE [22]. Both mechanisms converge into accumulation within the endosomes/lysosomes, interfering with the autophagic flux [19–21].

In addition to interfering with autophagic flux, the accumulation of CQ and HCQ within the endosomes/lysosomes can inhibits the post-translational modification of newly synthesized proteins within the endoplasmic reticulum or the trans-Golgi network vesicles (e.g, glycosyltransferases and proteases involved in the post-translational processing that requires low pH) [23] and blocking the processing of antigens [24,25].

Interestingly, autophagy has a double action in cancer therapy drugs can cause cytoprotective or cytotoxic autophagy effects. In addition, some chemoresistance in cancer therapy are related to cytoprotective autophagy [13]. Interestingly, CQ and HCQ are able to inhibit cytoprotective autophagy, leading to the sensitization of cancer cells to different chemotherapies.

Human cervical HeLa cells are resistant to the apoptosis-inducing effects of death receptors, but pretreatment with 75 μM of CQ sensitized HeLa cells to anti-Fas-mediated apoptosis, as measured by DNA breaks [26]. Moreover, CQ separately has no significant effect on the viability of HeLa cells, but it does increase the cytotoxic effects of cisplatin. Co-treatment also increased p62 expression, cleaved caspase-3 levels, caused inhibition downstream of autophagy and accumulation of Beclin-1 and LC3-II ubiquitinated misfolded intracellular proteins and simultaneous apoptotic activation. Since cisplatin induces the generation of misfolded proteins, but increases autophagy, this would alleviate the physiological stress of the endoplasmic reticulum by clearing the ubiquitinated proteins, which would trigger intrinsic apoptosis in HeLa cells [27].

The antitumor effects of 5-fluorouracil (5-FU) upon human colorectal adenocarcinoma HT-29 cells were also increased by CQ because it alters the action profile of 5-FU, while 5-FU downregulates the expression of p21 and p27. The pre-treatment of HT-29 cells with CQ inhibited this downregulation and decreased the expression of CDK-2 and activity of cyclin E/CDK2 complex, which probably cause the cell cycle arrest at phase G_0/G_1. Moreover, inhibition of colony-forming ability was observed when co-treatment was carried out [28]. Obviously, these observations assume that the autophagic process may be a defensive event against 5-FU-induced antiproliferative effect.

CQ plus sunitinib, bevacizumab and/or oxaliplatin increased

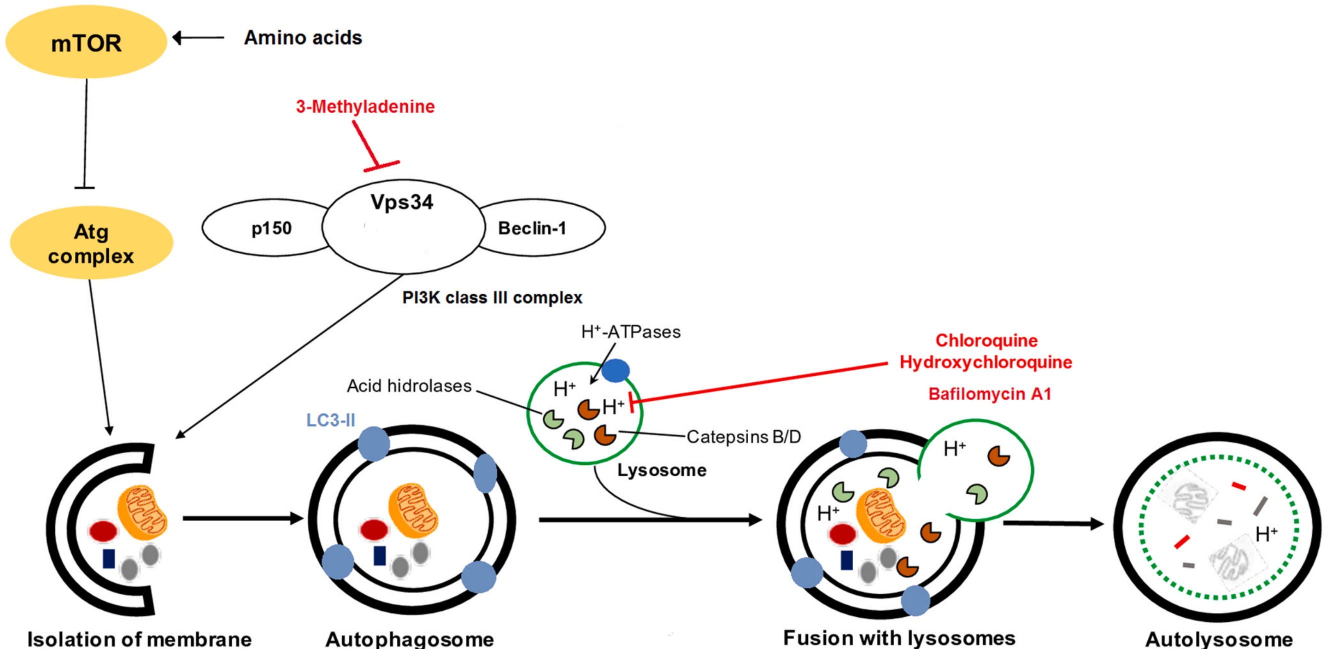

Fig. 1. Molecular mechanisms of autophagy.

intracellular levels of p62, indicating accumulation and interruption of autophagic flux. Increased caspase-3 activity and sensitivity under hypoxic conditions and reduced blood vessel formation, CD34 expression, microvessel density and nitric oxide levels were also observed in colorectal cancers [29,30].

CQ or HCQ also improved the antiproliferative and anticlonogenicity of trans retinoic acid in MCF-7 cells [31]. Mammospheroids in 3-D cultures also demonstrated additive inhibitory affects when CQ 50 μM and everolimus 20 nM were used. Increased p53 and p21 levels following treatment of MCF-7 cells with CQ, but not everolimus, have been observed [32].

2.2. Non-autophagy-related mechanism

In different type of cancer and non-cancerous cells and in a wide range of concentrations, the antitumor mechanism unrelated to autophagy has also been reported for CQ and HCQ.

Although it was observed higher lysosomal pH after 4 h of treatment with CQ and HCQ, higher pH values were sustained no more than the compound exposure time and renewal acidic organelles with low pH between 4 and 5 and 24 h indicated restoring of pH, which was also confirmed by nuclear translocation of transcription factors involved in lysosomal biogenesis, bigger lysosomal volume and returning of cathepsin levels in order to reestablish optimal conditions for enzyme digestion [33–35]. These data indicate that autophagy inhibition is not the only mechanism of CQ and HCQ.

Chloroquine sensitization of some breast cancer lines revealed to be independent of autophagy inhibition, since sensitization was not mimicked by the knockdown of *ATG12* or *BECLIN1* genes or following treatment with bafilomycin A1. CQ-induced cell death occurred even in absence of normal *ATG12* [36], proposing that reducing autophagy does not affect drug cytotoxicity ubiquitously in all human cells. In a similar way, most investigations indicate CQ does not block all forms and steps of the endolysosomal system.

Considering the arguments above, other targets of CQ and HCQ may lead to antitumor mechanisms unrelated to autophagy. This includes the activation of apoptosis and necroptosis, but the data are still contradictory. Curiously, some data indicate the role of the release of cathepsins B and D in the cytosol due to lysosomal alkalinization [37,38] as responsible for the induction of these programmed cell deaths.

Chloroquine inhibits *in vitro* growth of glioma cells (U87MG, G120, G130, G44, U251 and G112), but the wild-type p53 cell lines (U87MG and G120) were more sensitive to the growth suppression when compared to null (G130), truncated (G44) or with *TP53* inactivating mutations (U251 and G112). Not coincidently, caspase-3 activation and CQ-induced DNA fragmentation were greater in wild type p53 glioma cells, suggesting a function of p53-related pathways to activate apoptosis because the CQ-activated p53 transcriptional response was effective to induce genes involved in p53 regulation and cell cycle control/DNA repair (Hdm2 and p21) and also for the activation of apoptotic gene targets of p53 (pig3 and bax) (Fig. 2). Next, mice intracranially implanted with U87MG gliomas treated with CQ demonstrated

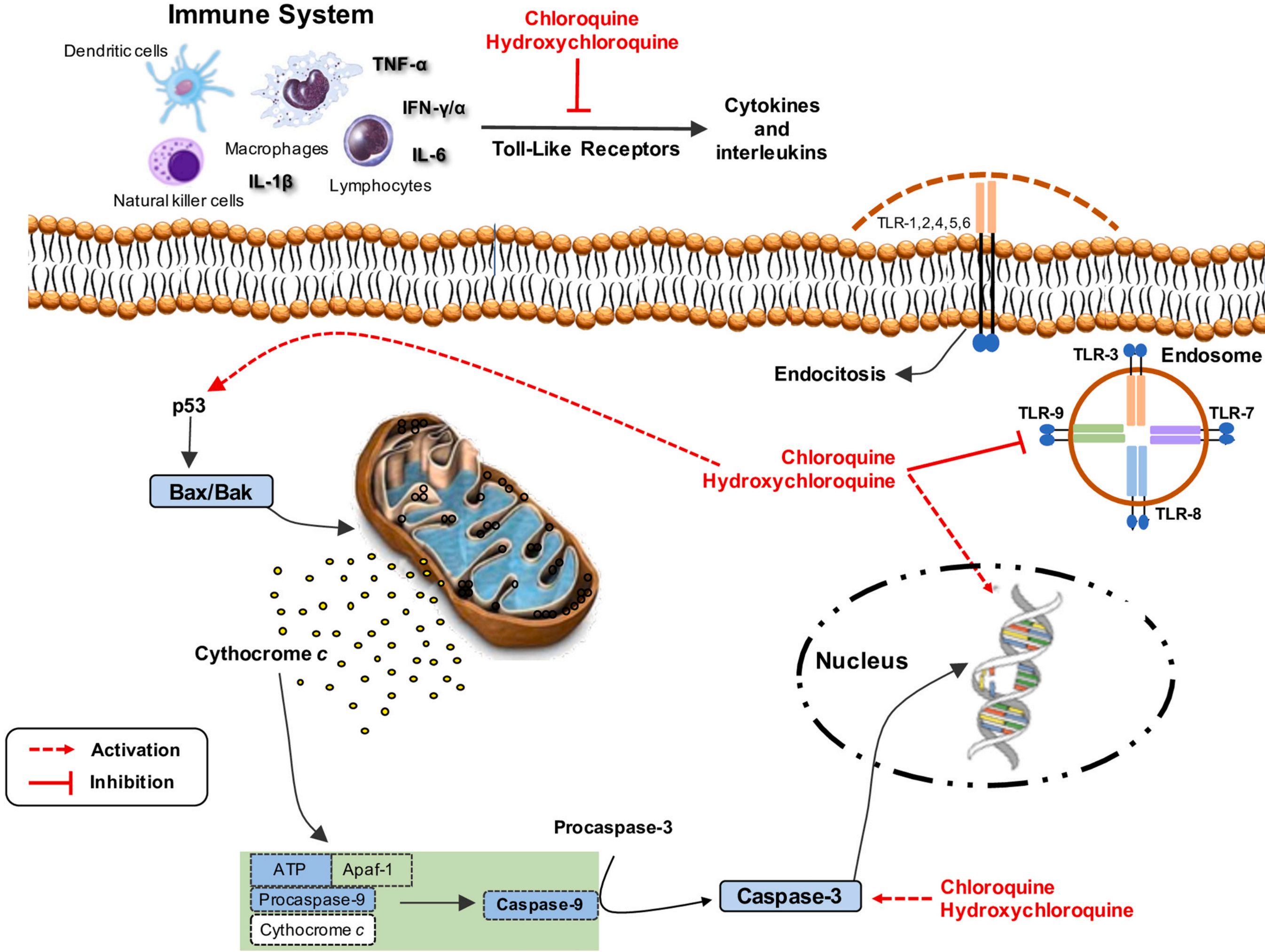

Fig. 2. Some non-autophagy-related mechanisms activated by chloroquine and hydroxychloroquine.

reduced tumor volume and mitosis and augmented apoptotic index, confirming *in vitro* data and demonstrating that CQ is an effective suppressing compound capacity of inducing apoptosis *in vivo* [39].

In untransformed wild-type telencephalic neurons, CQ caused the accumulation of autophagosomes and caspase-3 activation. Interestingly, cell death was inhibited by 3-MA, but not by BOC-aspartyl(OMe)-fluoromethyl ketone (BAF), a broad-spectrum caspase inhibitor. Additionally, CQ cytotoxicity was not blocked in knockout neurons for caspase 3 and 9 [40]. BAF, at 100 μM, had slight effects in attenuating CQ-induced death in U251 cells, despite its ability to completely inhibit caspase-3 activity [38]. A collapse of the mitochondrial membrane potential caused by CQ was similar in wild-type or mutated p53 glioma cells, which implies that mitochondrial dysfunction may also be a consequence of effects of a p53-independent pathway [41]. In addition, exposure to 50 μM of CQ for 24 h affects the intracellular localization of cathepsin D as observed by a diffuse cytoplasmic immunoreactivity in LN308 cells, while 75 μM of CQ in U87 cells produced changes in cathepsin D processing, as seen by the decrease in the active form of 28-kDa of cathepsin D, suggesting a direct or indirect action on its metabolism [38].

A well-known post-translational modification mediated by ataxia telangiectasia-mutated (ATM)/ataxia telangiectasia and Rad3-related (ATR) kinases during the cellular response to DNA damage to stabilize p53 tetramers by phosphorylation on a serine residue at position 15 does not appear to be an essential step because the signals ATM-dependent DNA damage may seem dispensable for the activation of p53 and caspases by CQ in some cell types, including glioblastomas [39,41–44]. Thus, at least for some glioma cell lines, CQ induces death regardless of its p53 status and exposure for 24 h to 50 μM of CQ decreases the viability of U87 (intact *TP53* gene), as well as *TP53* deficient LN308 cells and also causes caspase-3 activation in U251, LN229, and U118 cell lines with mutations in the transcriptional defect *TP53* genes [39].

HeLa cells treated with 30–90 μM of HCQ showed an increase lysosomal volume and cathepsin B release from lysosomes to the cytosol and nucleus, resulting in cytoplasmic vacuolization, cellular shrinkage, exposure of phosphatidylserine, loss of mitochondrial transmembrane potential, release of cytochrome c, activation of caspase-3 and condensation of chromatin. In particular, vacuolization was found before chromatin condensation and was accompanied by signs of macroautophagy. These effects were blocked by bafilomycin A1, showing that HCQ activated apoptosis via lysosomes and not via other organelles [37].

CQ showed concentration-dependent cytotoxicity upon mouse cell lines (colorectal carcinoma CT-26, melanoma B16-F10 and mammary carcinoma 4T1) overexpressing the receptor-interacting protein kinase 3 (RIP3). It upregulated the endogenous expression of RIP3 in CT-26 cells. Caspase-8-regulated RIP3, inhibitors of apoptosis (IAPs) and FLICE-like inhibitory protein, in association with the activation/increase of cathepsin D and caspases, lead to the accumulation of RIP3-p62 complexes after exposure to CQ in 10 and 75 μM. CT-26 cells treated with CQ showed fragmented nuclei, swollen organelles and ruptures of the cell membrane. These findings suggested that, instead of apoptosis, RIP3-dependent necroptosis was probably one of the reasons for CQ-induced cell death [45]. This was confirmed by phosphorylated mixed lineage kinase domain-like (pMLKL), a crucial component for necroptotic death. After all, mRIP3-Ser-232 phosphorylation sites are important for interaction between mRIP3 and mMLKL and also represent the signaling of conserved transduction necroptosis in humans and mice [46,47].

2.3. Immunological features

Among immunomodulatory actions, CQ and HCQ has been reported to inhibit the Toll-Like Receptor (TLR) signaling cascade (Fig. 2), obstructing the TLR-7 and TLR-9 signaling pathways by directly inhibiting CpG-TLR9 ectodomain interactions. They interfere with the secretion and production of inflammatory cytokines by mononuclear, dendritic and natural killer cells, including interleukins (IL-6, IL-1), interferon-gama/alpha (IFN-γ/α) and tumor necrosis factor-alpha (TNF-α), and expression of TNF receptors in macrophages, T cells and B lymphocytes [7,21,24,25,48,49]. CQ also inhibits the release of proinflammatory cytokines through TLR-7 or TLR-9 in activated peripherical blood mononuclear cells, containing dendritic and lymphocyte B cells, when in contact with antibodies and endogenous nucleic acids from patients with systemic lupus erythematous [50]. Since acidic pH is a prerequisite of endosomal TLR activation, the inhibitory activity of CQ and HCQ has been attributed to the alkalinization of endosomal vesicles [51,52].

On the other hand, THP-1 cells (human monocytic cell line that can differentiate to macrophage) treated with CQ displayed impaired competence to remove the bacteria *Francisella tularensis* by autophagosomes [53]. Therefore, a multifaceted discussion arises because some studies have proposed that CQ and HCQ can impair the maturation of lysosomes and autophagosomes, decrease uptake of antigens and prevent complete degradation of antigen by dendritic cells [6,24]. This naturally causes protein leakage from lysosomes, reduction of protein degradation in the endosomes and interferes with the generation of $CD8^+$ T cells mediated-antitumor responses and class I major histocompatibility complex (MHC class I) epitope production in antigen presenting cells (APC). It can be a negative side effect because the generation of an effective $CD8^+$ T cytotoxic lymphocytes response to MHC class I is considered the most important step for any tumor immune rejection or attack process [54,55].

Evidence also suggests that autophagy is important for MHC class II-mediated autoantigen presentation by antigen-presenting cells for $CD4^+$ T cells. After increasing the pH of the endosomal compartments, CQ and HCQ impair the normal and physiological development of lysosomes/autophagosomes and inhibit antigen presentation [15,56]. Nevertheless, the amounts of these peptide/MHC complexes appear not to be compromised after pretreatment with CQ and have been paradoxically slightly increased, which indicates that the immune eradication in CQ-treated tumors is likely due to adaptations in the pathways of death of tumor cells or immunogenicity rather than changes in the cross-presentation apparatus of the tumor antigen [24].

CQ can also function as a preventive and therapeutic agent in conditions of polymicrobial sepsis without interfering with innate immunity [57]. The presentation of soluble antigens to $CD8^+$ T cells was effectively improved by endosomal acidification *in vitro*. Therefore, as lysosomotropic agents, CQ and HCQ cause escape of antigen from destruction by endosomal/lysosomal proteolysis and guarantee substrates for exporting the proteasome to the class I processing pathway [58,59], as there is intensification of the levels of ubiquitination and protein degradation by immunoproteasomes, which assist in the production and presentation of tumor-specific peptides and improve anticancer immune responses. This effect can rationalize how the destruction of CQ-mediated protein occurs in the endocytic degradation of maturing dendritic cells, as well as facilitating the export of antigen to the cytosol for proteasome-dependent processing [60].

When confronted, these findings suggest that CQ and HCQ: i) have effects on TLR metabolism, but depend on the type of cell and target receptor, since immune activation and the proinflammatory effects mediated by TLR-2 and −4 are not inhibited by CQ and HCQ at the level of ligand binding; ii) they can act as antagonists of TLR-9, which can exhibit specific protective organ action, but not necessarily TLR inhibition is dependent on endosomal pH because they affect endosomal TLR activation directly by interacting with TLR ligands; iii) they do not attack all target receptors and many of them remain preserved and are not completely transcriptionally inhibited by CQ and HCQ; iv) do not compromise the presentation of antigen and MHC complexes; and v) it can prevent degradation of the antigen by dendritic cells, but facilitate the transport of the antigen to the cytosol for processing the proteasome, findings that rationalize the indication of CQ and HCQ, mainly, as

adjuvant options for cancer therapy.

3. Is there antitumor resistance?

Drug resistance has been a common problem in the treatment of cancer [2,61] and malaria [62,63]. CQ specifically kills malaria trophozoites by inhibiting heme polymerase, causes toxic amounts of accumulated free heme [64]. This drug has been used for a long time to treat malaria and the significant amount of drug resistance of *Plasmodium falciparum* has raised new questions and challenges in adapting cancer cells to escape of CQ and HCQ actions.

Cancer cells may have cross-resistance to various drugs with different structures or mechanism of action, a phenomenon known as multidrug resistance (MDR). The P-glycoprotein (P-GP) is a product of the MDR1 (ABCB1) gene and acts as a pump through the lipid bilayer of cancer cells to remove cytotoxic drugs and many commonly used pharmaceuticals. Another mechanism involved in drug resistance of cancer cells is the efflux of drug mediated by ATP-dependent pumps. These pumps belong to a family of ATP-binding cassette (ABC) carriers [61,65].

Resistance to CQ was associated to two molecular markers of the parasite: *P. falciparum* multidrug resistance-1 (Pfmdr-1) gene located on chromosome 5 [66] and *P. falciparum* CQ resistance transporter (Pfcrt) gene located on chromosome 7 [67]. Interestingly, Pfmdr-1 has homology to the mammalian multidrug resistance (MDR) genes [63]. P-glycoprotein is found in the digestive vacuoles of *P. falciparum* and operates to transport the cytoplasm vector to the vacuolar lumen [68]. Wide-type P-glycoprotein homolog 1 (P-gh1) gene increases the accumulation of CQ in the digestive vacuole and mutations in P-gh1 inhibit its function and therefore reduce the amount of CQ in the digestive vacuole. Instead, the Pfcrt gene, which also resides in the parasite's digestive vacuole, causes the vacuole's CQ efflux in its mono- or di-protonated forms [67]. Both mechanisms result in a marked reduction of CQ and HCQ in the parasite [63,69].

Although the role of P-gh1 in the resistance of cancer cells is not modulated by these drugs, extra ways to overcome the antitumor effects of CQ have been described. The knockout of autophagy-related genes, *ATG5* and *ATG7*, in human H-292 mucoepidermoid pulmonary carcinoma [70] and in ovarian cancer stem cells [71] resulted in cell survival. These genes encode the E1-like activating enzyme, a catalytical protein essential for transport of cytoplasmic vacuoles. The cells prevent the loss of proteins from autophagy and therefore gain resistance mainly due to the overloading of nuclear factor erythroid 2-related factor 2 (NRF2), a signaling cytosol necessary to compensate for the decrease in proteasome renewal in clones deficient in autophagy. Likewise, the growth of the wild-type H-292 tumor *in vivo* was inhibited by HCQ. However, tumors derived from $Atg7^{-/-}$ clones showed no sensitivity to HCQ and maintained growth. In fact, resistance to CQ and HCQ does not seem to be related to the elevation of NRF2, since autophagy-dependent cells of BT549 ductal breast carcinoma expressing NRF2 exogenously at levels similar to $ATG7^{-/-}$ clones showed a decrease in apoptosis after exposure to CQ [70]. In a subsequent study, an upstream autophagy regulator (RB1CC1/FIP200) was knocked out in BT-549 cells and RB1CC1 knockout clones developed autophagy resistance. Obviously, these both genetic conditions (Atg7 and RB1CC1 knockout clones) were less sensitive to CQ [72]. In any case, overexpression of NFR2 and a corresponding decrease in reactive oxygen species are obvious mechanisms by which cancer cells overcome the loss of upstream autophagic regulators [73].

4. Clinical trials

In vitro and *in vivo* tests have demonstrated the efficacy of CQ and HCQ on a great diversity of experimental models. These results stimulated the development of clinical trials (Table S1). Of 63 clinical trials, including those not yet recruiting, recruiting, enrolling by invitation, active but not recruiting, suspended, terminated, completed, withdrawn or with unknown status, the most frequently target tumors were those placed in the central nervous system (9 clinical trials), lungs (7), breast (7), pancreas (6), leukocytes (6), skin (4), and colon/rectum (4) (Fig. 3), in combination with a variety of traditional chemotherapeutic or immunotherapeutic agents or radiotherapy as well as using HCQ or CQ as monotherapy [74].

4.1. Glioblastomas

Glioblastoma multiforme (GBM) tumors arises from cells called astrocytes that support nerve cells. They are the most common and most aggressive type of cancer from brain or spinal cord. Treatments can be very difficult, but may slow progression of the cancer and reduce signs and symptoms. The development of mutations and the acquired resistance to chemotherapy are very common barriers for appropriate clinical practice [75]. In the first clinical trial with chloroquine as adjuvant to treat GBM, 18 patients underwent standard treatment with surgery, chemotherapy and radiation. Nine of them received 150 mg of chloroquine daily from day 1 after surgery and continued during the period of observation (22–50 months). At the end, patients from control group did not survive more than 22 months after surgery, four chloroquine-treated patients (46%) were alive, and four patients showed tumor remission after 2–4 years [76].

Similar results (NCT00224978) were found in another study in which 30 (15 + 15) patients with surgically confined GBM were randomly assigned to CQ (150 mg/day, orally) and placebo groups, and treatment started on day 5 postoperatively for 12 months. Median survival after surgery was 24 months for with CQ-treated patients and 11 months for control. Despite the small sample size, CQ improved medium-term survival when administered with conventional therapy [77], which indicates sensitizing effects can be attributed to antimutagenic actions, reducing the extent of the primary DNA rearrangements responsible for the appearance of mutant clones, though it alone has not demonstrated cytotoxic action.

Since preclinical studies indicate HCQ can augment the efficacy of DNA-damaging therapy by autophagy inhibition, a clinical trial (NCT00486603) evaluated the efficacy of HCQ in combination with radiation therapy and temozolomide. Although markers demonstrated inhibition of autophagy, no significant therapeutic benefit was detected [78]. One possibility would be to increase the dose, but the dose escalation carried out at the beginning of the study revealed that HCQ dosage > 600 mg/day resulted in adverse effects of grades 3 and 4, making it clinically unworkable.

The access to the central nervous system is difficult and there is a risk of developing resistance if metastases are exposed to low concentrations of chemotherapeutic drugs [79]. Safety and efficacy of radiosensitization was analyzed using CQ 150 mg for 4 weeks and 30 Gray irradiations in 10 fractions over 2 weeks in patients with brain metastases (NCT01894633) and this clinical trial improved control of brain metastases but did not enhance response rate or overall survival [80].

4.2. Pancreatic adenocarcinomas

Pancreatic adenocarcinoma is a lethal disease with increasing incidence. It is generally identified in advanced stages, which contributes to low survival rates and high possibility of metastases. Treatment is difficult and with few therapeutic options [81].

In the clinical trial NCT01273805, 20 patients with metastatic pancreatic cancer received HCQ (800–1200 mg/day) daily but monotherapies showed inefficacy to inhibit autophagy and therapeutic outcomes were clinically insignificant [82]. The combination of CQ and gemcitabine (NCT01777477) in patients with metastatic or unresectable pancreatic cancer revealed noteworthy results [83]. Thirty-five patients with pancreatic adenocarcinoma were included in the study (NCT01128296) to assess preoperative treatment with gemcitabine

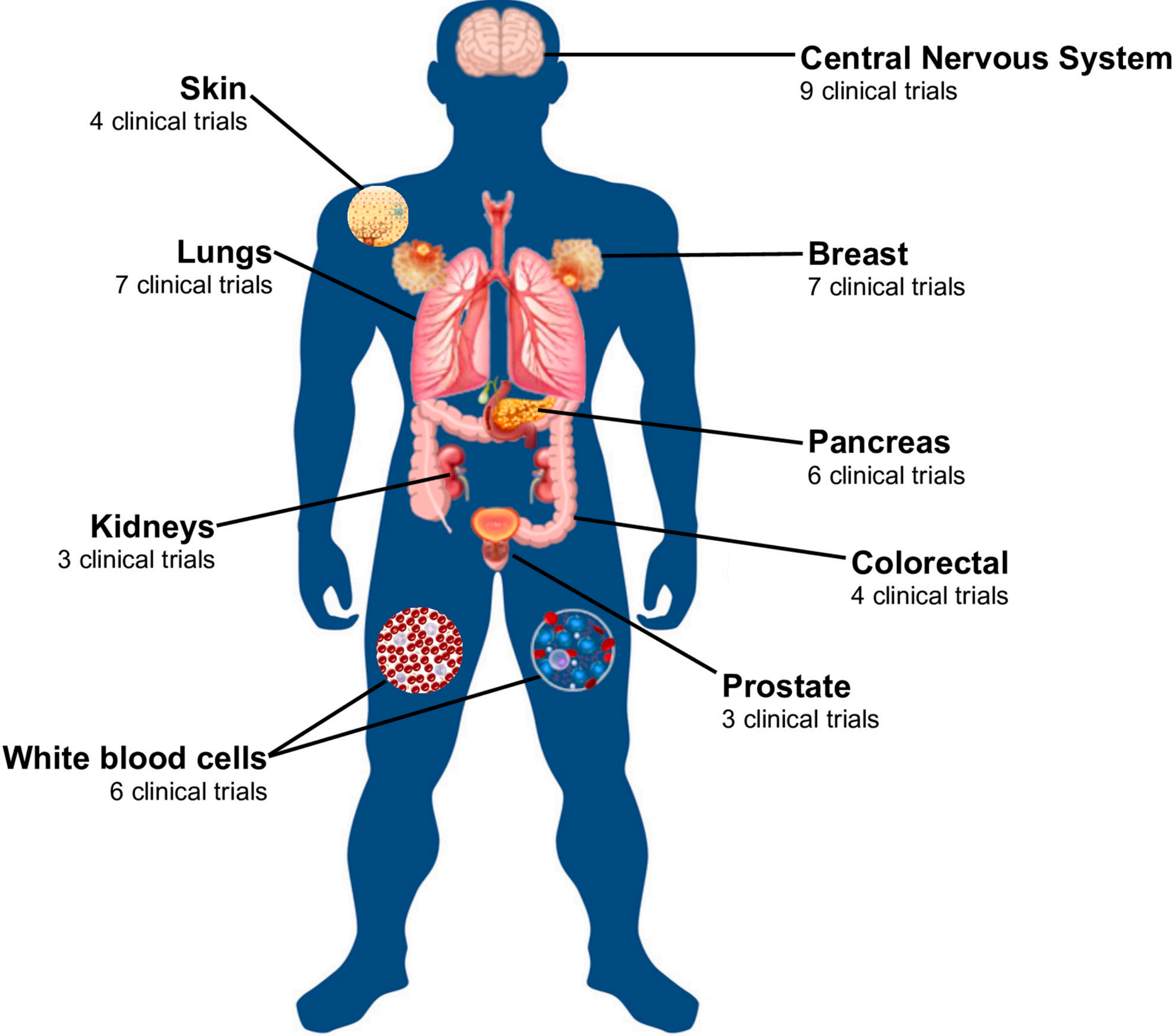

Fig. 3. Main anticancer targets in clinical trials using chloroquine and hydroxychloroquine.

(1500 mg/m^2) plus HCQ. Two fixed doses of gemcitabine were administered on days 3 and 17 in combination with oral HCQ 1200 mg/day for 31 consecutive days until the day of surgery. Nineteen patients (61%) had a decrease in tumor marker CA-19–9 and superior median overall survival (34.83 vs. 10.83 months, $p < 0.05$). Surprisingly, this study demonstrated a relationship between treatment and increase in tumor markers. Patients who showed increase > 51% in LC3-II levels identified in peripheral blood mononuclear cells also showed progress in disease-free survival (15.03 vs. 6.9 months, $p < 0.05$) [84]. This favorable data encouraged the development of the phase II clinical trial (NCT01978184), and inclusion of nab-paclitaxel should improve treatment of resectable pancreatic adenocarcinomas. Other clinical trial with 112 patients (NCT01506973) using the same drugs in patients with advanced pancreatic cancer indicated that addition of HCQ to block autophagy did not alter the overall survival [85].

5. Conclusions

Chloroquine and hydroxychloroquine cause accumulation of acidic vesicular organelles and interrupt autophagosome-lysosome fusions. This explains, at least in part, their sensitizing effects of chemotherapy when used as an adjuvant option in clinical trials against cancer. Additionally, they also have antitumor mechanism unrelated to autophagy, including cell death from apoptosis and necroptosis and immunomodulatory/anti-inflammatory characteristics. However, the link between some anticancer mechanisms, clinical efficacy and pharmacological safety observed *in vivo* has not yet been fully defined.

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Authors contribution

PMPF planned the review, wrote autophagy section, and revised the article. RWRS edited the article and designed illustrations. GCGM commented about mechanisms of antitumor resistance. JROF presented clinical data. DPB assisted in autophagy section and final editing. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could influence this work and outcomes reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2021.105582.

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Drug Repurposing in Anticancer Therapy

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Description

In cancer development, cells acquire multiple mutations which contribute to full malignancy. Resistance of tumour cells are associated with alterations in receptors (e.g., human epidermal receptors (HER/ErbB), G-protein-coupled receptors (GPCRs), intracellular receptors (AR, androgen receptors, estrogen receptors (ER); GR, glucocorticoid receptors (GR), thyroid hormone receptor (TR) and channel-linked receptors). The activation of erythroblastic leukemia viral oncogene homologue (ErbB) receptors is initiated by signalling pathways such as the rat sarcoma/rapidly accelerated fibrosarcoma/ mitogen-activated protein kinase kinase/extracellular signal-regulated kinase ½ (RAS/ RAF/MEK/Erk1-2) signalling pathway. Other signalling pathways include phosphatidylinositol 3-kinase/protein kinase B (PI3-K/AKT) and Janus kinase/signal transducers and activators of transcription (JAK/STAT). These receptors can affect the cell cycle, cytoskeleton reorganization, apoptosis, metastasis,

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Furthermore, drug redirection offers the opportunity to identify therapeutics or medications for the treatment of rare diseases, including some types of cancers. Moreover, this can save time and money, thus improve productivity. Finally, drug redirection can reduce the risks and resources associated with the development of new drugs. It can provide valuable knowledge of the commercial availability of drugs. Previous records allow access to computational tools, pharmacodynamic, toxicokinetic, and clinical databases, enabling faster reusable drugs.

This Special Issue aims at highlighting the latest studies discussing the mechanisms of antitumor molecules/formulations under preclinical studies or clinical trials. Submissions can also include alternatives to overcome the pharmacological and toxicogenetic problems of promising repurposing drugs. We invite researchers to contribute with original research and review articles about nonclinical and clinical/translational studies focusing on new antitumoral options to improve patient's survival, quality of life and reduction of organ-specific toxicities.

Potential topics include but are not limited to the following:

- Pharmaceutical reuse of traditional drugs focusing on antitumour therapies
- Cellular and molecular mechanisms of tumour resistance to chemotherapy, radiotherapy, and/or immunotherapy
- In vitro and in vivo antitumor mechanisms of angiogenesis inhibition in solid tumours
- Receptors, relapse and oncopharmacology of solid tumours
- Oncological challenges in translational medicine for natural, semi-synthetic, or synthetic compounds
- Nonclinical protocols in experimental oncology
- Clinical findings of anticancer studies with reusable drugs
- Main factors that contribute to the ban of certain antitumor drugs from the market or clinical trials
- Biological differences between species with absorption, distribution, metabolism, excretion and toxicity (ADMET) parameters
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Review Article

Aminoquinolines as Translational Models for Drug Repurposing: Anticancer Adjuvant Properties and Toxicokinetic-Related Features

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The indiscriminate consumption of antimalarials against coronavirus disease-2019 emphasizes the longstanding clinical weapons of medicines. In this work, we conducted a review on the antitumor mechanisms of aminoquinolines, focusing on the responses and differences of tumor histological tissues and toxicity related to pharmacokinetics. This well-defined analysis shows similar mechanistic forms triggered by aminoquinolines in different histological tumor tissues and under coexposure conditions, although different pharmacological potencies also occur. These molecules are lysosomotropic amines that increase the antiproliferative action of chemotherapeutic agents, mainly by cell cycle arrest, histone acetylation, physiological changes in tyrosine kinase metabolism, inhibition of PI3K/Akt/mTOR pathways, cyclin D1, E2F1, angiogenesis, ribosome biogenesis, triggering of ATM-ATR/p53/p21 signaling, apoptosis, and presentation of tumor peptides. Their chemo/radiotherapy sensitization effects may be an adjuvant option against solid tumors, since 4-aminoquinolines induce lysosomal-mediated programmed cytotoxicity of cancer cells and accumulation of key markers, predominantly, LAMP1, p62/SQSTM1, LC3 members, GAPDH, beclin-1/Atg6, α-synuclein, and granules of lipofuscin. Adverse effects are dose-dependent, though most common with chloroquine, hydroxychloroquine, amodiaquine, and other aminoquinolines are gastrointestinal changes, blurred vision ventricular arrhythmias, cardiac arrest, QTc prolongation, severe hypoglycemia with loss of consciousness, and retinopathy, and they are more common with chloroquine than with hydroxychloroquine and amodiaquine due to pharmacokinetic features. Additionally, psychological/neurological effects were also detected during acute or chronic use, but aminoquinolines do not cross the placenta easily and low quantity is found in breast milk despite their long mean residence times, which depends on the coexistence of hepatic diseases (cancer-related or not), first pass metabolism, and comedications. The low cost and availability on the world market have converted aminoquinolines into "star drugs" for pharmaceutical repurposing, but a continuous pharmacovigilance is necessary because these antimalarials have multiple modes of action/unwanted targets, relatively narrow therapeutic windows, recurrent adverse effects, and related poisoning self-treatment. Therefore, their use must obey strict rules, ethical and medical prescriptions, and clinical and laboratory monitoring.

1. Introduction

Globally, about 1 in 6 deaths is due to cancer and about 70% of cancer deaths occur in low- and middle-income countries. Approximately, one third of these deaths are associated with high body mass index, low consumption of fruits and vegetables, lack of physical activity, and use of tobacco and alcohol. Tobacco use is the most important risk factor for cancer and accounts for approximately 22% of the total deaths. On the other hand, infections such as hepatitis and human papilloma virus (HPV) are responsible for up to 25% of cancer cases in poor and developing countries. In 2018 alone, approximately 9.6 million deaths were related to cancer [1–3].

Determining treatment and palliative care goals are critical steps for cancer therapy with integrated and people-centered health services [3]. Even with a variety of options to treat sarcomas, carcinomas, and adenocarcinomas, such as antimetabolites, microtubule inhibitors, DNA intercalators [4], and monoclonal antibodies [5], resistance remains the cause central to therapeutic failures as well as adverse side effects [6].

In this context, the synthesis and identification of strategic molecules is essential if we want low cost, efficiency, and speed in the production of valuable chemotherapy molecules. Here, we can include aminoquinoline compounds that have the amino group at position 4 of the quinoline ring system. These compounds include molecules used in the treatment of first line (amodiaquine and chloroquine), recurrence (tafenoquine), uncomplicated (hydroxychloroquine) and prevention (chloroquine, hydroxychloroquine and tafenoquine) of malaria infections by *Plasmodium vivax*, *P. malariae*, *P. ovale*, and *P. falciparum* [7–9].

In December 2019, a new severe acute respiratory syndrome coronavirus-2 (called SARS-CoV-2) emerged in China and led to the coronavirus-related pandemic in 2019 (COVID-19) [10]. The indiscriminate use of chloroquine and hydroxychloroquine as a first-line, adjuvant, or palliative drug(s) to treat victims of COVID-19 or to control new local outbreaks as a prophylactic [11, 12] emphasized the various longstanding clinical branches of drugs, including those against chronic disorders. Advantages such as low cost, long usage history, and market availability even in developing countries where malaria is endemic are reasons that explain, at least in part, the commercial triumph of these drugs, converting 4-aminoquinolines into "star drugs" for their reuse in the pharmaceutical industry. Then, we performed a review on the anti-tumor mechanisms of aminoquinolines, focusing on the responses and differences of histological tumor tissues and on the aspects of toxicity related to pharmacokinetics.

To carry out a comprehensive and consistent analysis, we use only primary and secondary materials, including research articles, reviews, books, and government publications written in English, Portuguese, or Spanish. The bibliographic research was performed in the scientific databases ScienceDirect, Scopus, PubMed, and Scielo. The descriptors "autophagy," "cell cycle," "apoptosis," "drug repurposing", and "anti-tumor" were combined with "aminoquinoline" for a narrative scientific exploration.

2. Main Text

2.1. Drug Repurposing for Anticancer Agents: Need or Pharmaceutical Business? Less toxic and more effective treatment designs are often the main reasons for redirections, considering previously recorded aspects of preclinical and clinical pharmacodynamics and toxicokinetics, making drug reuse faster [13–15].

Examples of reuse of effective anticancer drugs in advanced preclinical or clinical studies are almost immeasurable. As a typical example, thalidomide is a leading molecule that has been marketed in 1956 in West Germany, first as antiflu and in 1957 as an antiemetic for pregnancy, but has now been repurposed and approved for multiple myeloma [16, 17]; itraconazole, a triazole antifungal developed in the 1980s, showed anticancer activities in preclinical *in vitro* and *in vivo* models of pancreatic ductal adenocarcinoma derived from liver metastasis [18]; disulfiram, initially approved to mitigate alcoholism, has been investigated to treat radiation-resistant breast cancer stem cells [19]; nelfinavir, originally indicated for the treatment of HIV infection, also exhibits synergistic effects against human cervical cancer cells [20]; sildenafil, which failed in phase II clinical trials for angina disorders, has been redirected to the treatment of erectile dysfunctions and sensitizes prostate cancer cells to doxorubicin-mediated apoptosis [21]; mebendazole, a broad spectrum anthelmintic developed for the treatment of veterinary parasites, has advanced from the treatment of animals to the first clinical applications in humans, inhibiting the growth of adrenocortical carcinoma, gastric cancer, medulloblastoma, glioblastoma, leukemia and myeloma, and breast and prostate cancers [22]; metformin, a classic hypoglycemic medication for diabetes, has revealed a new identity as an antitumor activity by suppressing the mammalian target of rapamycin (mTOR) in human cervical cancer [20] and acute myeloid leukemia [23], and valproic acid, an anticonvulsant that has been considered in several clinical trials due to its epigenetic properties, inhibition of histone deacetylase, and induction of autophagy in neoplastic stomach cells [24].

In 1934, the first synthetized aminoquinoline—chloroquine [4-N-(7-chloroquinolin-4-yl)-1-N,1-N-diethylpentane-1,4-diamine]—was based on the quinine structure isolated from Cinchona officinalis barks in the 1800s. In 1946, hydroxychloroquine [2-[[(4S)-4-[(7-chloroquinolin-4-yl) amino]pentyl]-ethylamino]ethanol] was synthesized, and both molecules were developed as antimalarial tools (Figure 1), as well as extra 4- and 8-aminoquinolines (amodiaquine, tafenoquine, primaquine, mefloquine, quinacrine, quinine, quinidine, and 8-hydroxyquinoline and artemisinin) in an attempt to overcome resistance in *Plasmodium* species, and the side effects [8, 25, 26] seem similar to that of cancer therapy, whose initial successful single-target therapies have been replaced by more combined efficient protocols.

Currently, the aminoquinolines, chloroquine phosphate and hydroxychloroquine sulphate, have been the most

Figure 1: Structures of some common aminoquinolines in clinical use as antimalarials or anti-inflammatory drugs and under investigations as anticancer agents.

common salts used [27] as the first-line regimen for the radical cure of malaria by *P. vivax* in most regions [26] and to treat acute and chronic inflammatory conditions [9, 28–30], respectively, although primaquine and amodiaquine, when used alone or in combination with artemisinin, provide adequate efficacy against many chloroquine-resistant parasites [8, 26].

2.2. Antiproliferative Mechanism of Aminoquinolines. More than 50 years ago, chloroquine showed promising cytotoxicity of tumor cells *in vitro* [31], but only in the last two decades, studies with chloroquine, hydroxychloroquine, and related molecules demonstrated lysosomal-mediated cell death in cancer cells. The exact mechanism of cytotoxic action is not yet fully understood, but hypothesis have attempted.

These molecules can enter into endosomes/lysosomes by passive diffusion, or they can be taken up together with sodium in the exchange of protons, as demonstrated by specific inhibitors of eukaryotic membrane Na^+/H^+ exchangers (NHE) [32]. Both converge in the accumulation within endosomes/lysosomes, leading to the interference of the autophagic flux [33–35], disruption of several enzymes (e.g., acid hydrolases and cathepsin B and D lysosomal cysteine proteases) [36, 37], inhibition of antigen processing [38, 39], and post-translational modification of recently produced proteins [35, 40]. In addition, preclinical and clinical investigations are testing the effectiveness of quinines as inhibitors of the autophagy flux to overcome resistance when traditional chemotherapy drugs are used as monotherapy, since the induction of autophagy has been associated with resistance in the therapy of cancer [41, 42].

2.2.1. Brain Tumor Cells. Chloroquine decreases cell proliferation of p53 wild-type glioma lines more efficiently, indicating a key p53 responsibility for apoptotic cell death and cell cycle control through the HDM2, P21, PIG3, and *BAX* genes (Figure 2). Likewise, the induction of apoptosis *in vivo* was found in mice with U87MG glioma intracranially when treated with chloroquine [43].

On the other hand, chloroquine-induced neuronal cell death of normal neurons [44] indicates mitochondrial dysfunction as a result of p53-independent effects [43], but dependent on cathepsin D lysosomal cysteine proteases processing, proposing direct or indirect actions on the cathepsin D metabolism [37]. Moreover, chloroquine activation of ataxia telangiectasia-mutated (ATM)/ataxia telangiectasia and Rad3-related (ATR) kinase DNA injuries [45] seems unnecessary for caspases and p53 activation [37, 43, 44, 46–48], suggesting that aminoquinolines induce the death of glioblastoma cells, regardless of the p53 status [37].

The absence of DNA damage induced by chloroquine similar to DNA damage by direct ionizing radiation with consequent activation of p53 can be associated with its mechanism of interaction with DNA molecules, since chloroquine intercalates into DNA, but does not cause DNA damage directly [43, 49]; this does not exclude that caspase-3 activation is stronger in wild-type p53 glioma cells, proposing a clear contribution of p53 to chloroquine-induced apoptosis [43].

U251-MG brain cell line, orthotopic GL-261 gliomas, or rat brain-implanted C6 cells treated with suberoylanilide hydroxamic (histone deacetylase inhibitor, HDACi) and temozolomide (alkylating agent) in the presence of chloroquine 10–15 μM showed reduced cell viability, morphology changes, increase in the sub-G_1 population, Bax, cleaved-caspase-3, and cleaved-PARP1 [poly-(ADP-ribose)-polymerase 1], externalization of phosphatidylserine, and activation of caspase-3/7 (Table 1). Such events are features of apoptosis, but the time course curves showed that the

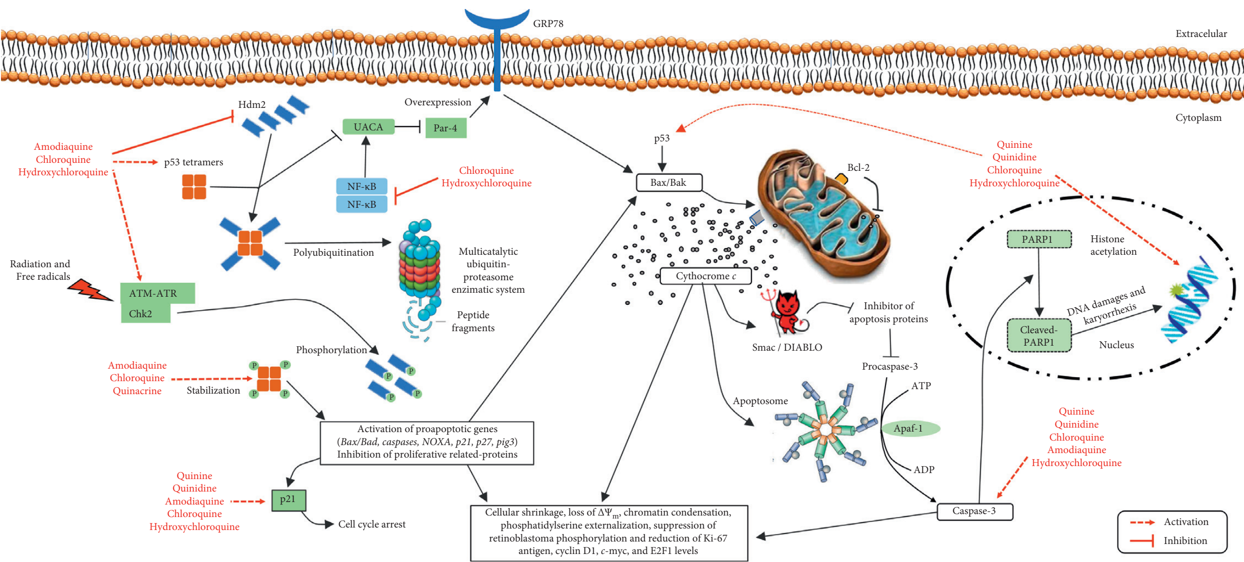


Figure 2: Pathways involved in general cytotoxicity and activation of apoptosis by 4-aminoquinolines. The transportation of both drugs is completely via passive diffusion (i.e., no transporters are involved). Bak and Bax are p53-induced proapoptotic members that constitute the apoptotic pore complex for the release of mitochondrial cytochrome c, leading to mitochondrial depolarization, activation of caspase-3, cleaving of poly-(ADP-ribose)-polymerase 1 (PARP-1), and nuclear DNA fragmentation. Aminoquinoline-dependent DNA damage activates p53 and its downstream gene p21, resulting in cell cycle arrest after a post-translational p53 activation by phosphorylation of the ataxia telangiectasia-mutated (ATM) protein, leading to ATM-dependent phosphorylation of p53 checkpoint protein kinase. Moreover, chloroquine, quinacrine, and amodiaquine trigger p53 stabilization in TP53-specific reporter human cancer cells and block the p53 ubiquitination properties of human double minute 2 (Hdm2) molecules, which in turn prevents p53 proteasome degradation. Stimulation of histone acetyltransferase (HAC) and inhibition of histone deacetylase (HDAC) are part of the rationale pattern of arresting growth. Chloroquine is linked to the activation of p53, inhibition of NF-κB (factor nuclear kappa B) and uveal autoantigen with coiled-coil domains and ankyrin repeats (UACA), which promotes secretion of prostate apoptosis response-4 (Par-4) and expression of glucose regulated protein 78 (GRP78) receptor on the cancer cell surface, and consequent apoptosis.

G_2/M arrest occurs with autophagy and before the apoptosis because the blocking of this response with autophagy inhibitors (3-methyladenine and chloroquine, for example) makes cells susceptible to temozolomide and suberoylanilide hydroxamic [54, 60].

2.2.2. Human Cervical Tumors. Human papilloma positive HeLa cells (p53 wild-type) are resistant to apoptosis-inducing effects of death receptors [64], but pretreatment with 75 μM chloroquine sensitized HeLa cells towards apoptosis mediated by Fas, as measured by TUNEL staining of DNA strand breaks [65], due to the disruption of mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK)1/2, as found in cells treated with PD98059, a MEK1 inhibitor. Indeed, chloroquine and analogues appear to disable members upstream of the MAPK pathway (Figure 3), avoiding ERK phosphorylation and activation by a paradoxical Raf phosphorylation in specific residues, which possibly blocks the ERK activation by Akt activity [65].

HELa cells treated with 10–30 μg/mL of hydroxychloroquine presented an increase in lysosomal volume and cathepsin B release from lysosomes to the cytosol and the nucleus, resulting in cytoplasmic vacuolization, cellular shrinkage, exposure of phosphatidylserine, loss of mitochondrial transmembrane potential ($\Delta\Psi m$), release of cytochrome c, activation of caspase-3 (Figure 2), and condensation of chromatin. In particular, vacuolization was found before chromatin condensation and was accompanied by the signs of macroautophagy [36]. These effects were blocked by bafilomycin A1, which prevents degradation of LC3, induces its accumulation in autophagolysosomes [66] and acts as an inhibitor of the vacuolar-type H^+-ATPase, changing endosomal pH [67], showing that hydroxychloroquine activated apoptosis via lysosomes instead of other organelles (mitochondria or nuclei, for example).

The colorimetric MTT assay indicated that 3-methyladenine (3-MA) or chloroquine separately has no significant effects on the viability of HeLa cells, but both enhance the cytotoxic effects of cisplatin. The cotreatment also increased the expression of p62, the levels of cleaved caspase-3/-4, caused inhibition of autophagy downstream, and accumulation of ubiquitinated beclin-1 and LC3II misfolded proteins, and almost simultaneous apoptotic activation. Since cisplatin induces the generation of misfolded proteins, but increases autophagy, this would alleviate the physiological stress of endoplasmic reticulum by clearing the ubiquitinated proteins, which would trigger intrinsic apoptosis in HeLa cells [55]. The compound 3-MA is an inhibitor of phosphatidylinositol 3-kinases, which play an important role in controlling the activation of mTOR, a key regulator of autophagy [68].

2.2.3. Colorectal Cancers. As a pyrimidine analogue, 5-fluorouracil (5-FU) acts as an antimetabolite to inhibit DNA

Table 1: General mechanisms of chemosensitizing and radiosensitizing adjuvant actions of chloroquine, hydroxychloroquine, and analogues.

Treatment/Drug	Adjuvant actions	References
Phosphatidylinositol analogs, oligopeptides Akt-PH linkers, inhibitors of Akt-kinase, and blockers of ATP-binding site catalytic subunit	Mediated chemosensitization and enhanced cytotoxicity	[50]
All-trans retinoic acid	Reduction of Ki67-positive cells and clonogenicity, activation of histone acetyltransferase, and inhibition of histone deacetylase enzymes	[51]
5-Fluorouracil	Down-regulation of CDK-2 expression and cyclin E/CDK2 complex activity, arrest in G_0/G_1 phase, and enhancement of antiproliferative properties	[52]
Everolimus	Proliferative reduction, increase of p53 and $p21^{Cip1}$ levels, phosphorylation reduction at serine 2448 in mTOR proteins	[48]
Rapamycin	Blockade of autophagy and LC3-II degradation, cytotoxic chemosensitization and involvement of a caspase-independent mechanism	[53]
Cisplatin	Increase of caspase-3 activation, LC3 II ubiquitinated intracellular misfolded proteins, and intrinsic apoptosis	[54, 55]
Docetaxel	Enhanced cytotoxicity and stronger *in vivo* anti-tumor efficacy	[56]
Doxorubicin	Potentiated cytotoxicity upon coexposure	[57]
Oxilaplatin	Increased sensitivity under hypoxic conditions and p62 levels, delaying of tumor growth of HT-29 colon cancer xenografts	[58]
Sunitinib	Increase of the p62 level, reduction of blood vessel formation, CD-34 expression, microvessel density, and nitric oxide levels in tumor, and Ehrlich ascites carcinoma tumor growth reduction	[59]
Temozolomide	Cell viability reduction and intensification of cleaved-caspase-3, cleaved-PARP1, phosphatidylserine externalization, and caspase-3/7 activation	[54, 60]
Receptor-interacting protein kinase 3 (RIP3)	Upregulation of RIP3, accumulation of RIP3-p62 complexes and type II-LC3B, and efficiency on colon tumor-bearing mice	[61]
Bevacizumab	Weakening of the Akt-mTOR signaling pathway and recovering the tumor-suppressive effect of bevacizumab	[62]
Sertraline + erlotinib	Amplification of caspase-independent autophagic cell death and mouse survival in orthotopic non-small cell lung cancer mouse models	[63]

and RNA synthesis, but it also has radiosensitizing, immunosuppressive, and mutational properties and has been widely used to treat various solid tumors, including colorectal, breast, stomach, pancreas, ovary, bladder, and liver cancers [69]. The apoptotic effects of 5-FU on human colorectal adenocarcinoma HT-29 cells were also increased by chloroquine. The pretreatment of HT-29 cells with chloroquine suppressed CDK-2 expression and catalytic activity of cyclin E/CDK2 complexes (Figure 2), leading to the (G_0/G_1) arrest [52]. Such findings suppose autophagy as a protective route against the action of 5-FU, since autophagic inhibitors increase the antiproliferative properties of this fluoropyrimidine.

Murine cell lines showing endogenous upregulation of receptor-interacting protein kinase 3 (RIP3) were more sensitive to chloroquine [61] and presented cytosolic accumulation of RIP3-p62 complexes and LC3-II, which is commonly recruited to phagosome membranes. However, initial/executioner caspase levels are apparently not altered by chloroquine during necroptotic cell death in CT-26 cells [61].

Since the morphological and flow cytometric investigations of chloroquine-treated CT-26 cells showed dissolved nuclei, condensation, swelling of organelles, and rupture of the cell membrane, these findings suggested that, instead of apoptosis, RIP3-dependent necroptosis was probably a reason for $RIP3^+$-chloroquine-induced cell death [61, 70, 71].

The induction of tumor apoptosis *in vivo* exposed that apoptosis is not the only way by which chloroquine activates death cascade, as verified by TUNEL experiments and signals of necroptosis. In any case, mice with a CT-26-tumor xenograft showed tumor reduction after adjuvant treatments, whereas chloroquine alone showed a 45% reduction, and the combination with chemotherapies increased by up to 80% [61].

Chloroquine plus sunitinib, bevacizumab, and/or oxaliplatin increased intracellular levels of p62, indicating the accumulation and interruption of autophagic flux, increased caspase-3 activity and sensitivity under hypoxia conditions, and reduced blood vessel formation, expression of CD31,

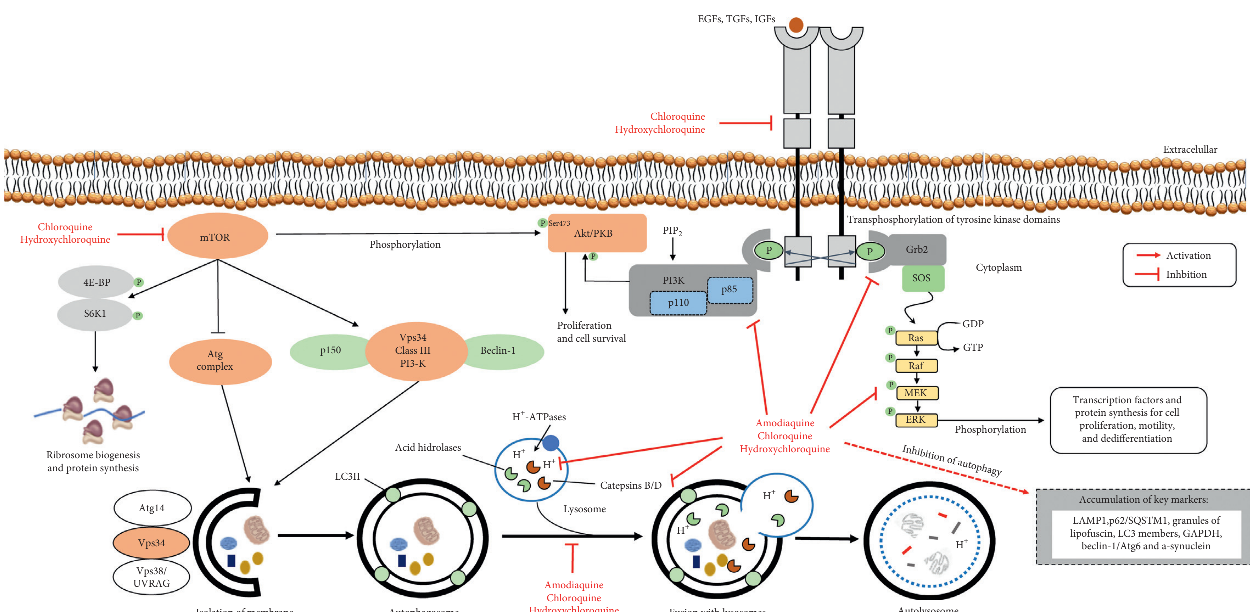


FIGURE 3: Molecular findings, which support the theory that chloroquine and analogues exerts, at least in part, antineoplastic effects altering the phosphorylation *status* of EGFR/PI3K/Akt/mTOR/Atg and p53 pathways, inhibiting directly PI3K-Akt and mTOR kinases, obstructing catalytic subunits in the ATP-binding site or altering the recycling of tyrosine kinase receptors, besides impairing or interfering in lysosomal and autophagosome functions. mTOR phosphorylates the eukaryotic initiation factor 4E-binding protein (4E-BP) and the p70S6 kinase1 (S6K1). Therefore, if specific drug inhibitors against mTOR kinase are used, this should not only have altered proliferation but also the protein synthesis rate. Vesicular protein sorting 34 (Vps34) complex I has Atg14p as an additional factor, which participates in the formation of autophagosomes, while complex II has Vps38, which is required for vacuolar protein sorting. These catalytic complexes work as ubiquitin-like conjugation systems for phagophore elongation and recruitment of other proteins to the self-digesting process, as seen with Vps34, a phosphatidylinositol serine-threonine kinase, its binding partner Beclin-1 (Atg6) and the protein kinase p150 in mammals (Vps15). Assembly of this complex is crucial for autophagy and it recruits other proteins to the phagophore assembly site (PAS). Therefore, the phagophore elongates into a cup-shaped structure and begins to engulf cellular material, sequestering the material in a double-membraned autophagosome. Both chloroquine and hydroxychloroquine block autophagy in initial phases, causing accumulation of acidic vesicle cell markers and appear to deactivate upstream members of mitogen-activated protein kinase (MAPK) pathway, preventing phosphorylation and activation of extracellular signal-regulated kinases (ERK)1/2 by a paradoxical phosphorylation of Raf at specific residues, which possibly blocks ERK activation by Akt activity.

microvessel density, and nitric oxide levels in colorectal cancers [58, 59]. The growth of HT-29 colon cancer xenografts in bevacizumab- and oxaliplatin-treated mice was postponed from 7.2 to 23 days when bevacizumab and oxaliplatin were coadministered with chloroquine [58].

In addition to acting as inhibitors of autophagy, chloroquine, quinacrine, and amodiaquine trigger p53 stabilization in TP53-specific reporter human cancer cells [59] and wild-type cell lines [49, 72] (Figure 2). Amodiaquine *in vitro* at 20 μM was specifically more efficient than chloroquine in inducing p53 stabilization by an independent ATM signaling pathway, interrupting cell proliferation of colorectal carcinoma cell lines (in addition to breast, hepatic, lung, sarcoma, and melanoma), decreasing the synthesis of a general ribosome precursor—47S rRNA—in U2OS cells, inducing the accumulation of LC3II autophagosome and lysosomal associated membrane protein 1 (LAMP1), and impairing translocation of the DDX21 nucleolar helicase to the nucleoplasma [49], the catalytic protein involved in the synthesis and processing of rRNA [73].

The nucleolar changes induced by amodiaquine were similar to those observed in cells treated with chloroquine and BMH-21l, a polymerase I inhibitor. Furthermore, amodiaquine inhibited the activity of ubiquitin ligase Hdm2's and thereby stabilized/activated p53 [49].

2.2.4. Breast Carcinomas. Quinidine [74–76], quinine [77], chloroquine [76, 77], and hydroxychloroquine [75] induced differentiation in MCF-7 cancer cells, as demonstrated by the accumulation of cells in the G_0 phase, intracellular milk fat globule membrane protein and lipid droplets (typical markers of differentiation), increased p21 and suppressed phosphorylation of retinoblastoma and expression of Ki-67 antigen, cyclin D1, *c*-myc, and E2F1 protein levels (Figure 2). While chloroquine was stronger in stimulating MCF-7 apoptosis, quinine was the most active in promoting differentiation [77].

Chloroquine or hydroxychloroquine + all-trans retinoic acid also reduced MCF-7 cells positive for Ki67, and their clonogenicity and hydroxychloroquine altered the acetylation *status* in the N-terminal lysines of the histones H3 and H4, epigenetic sites expected by the “zip”: model of histone acetylation [51]. These observations indicate that, in association with all-trans retinoic acid, quinidine, quinine, chloroquine, or hydroxychloroquine regulates protein

acetylation events and the combination with all-trans retinoic acid stimulates histone acetyltransferase and inhibits HDAC enzymes in breast cancers (Figure 2). Nevertheless, the direct inhibition of the HDAC enzyme does not appear to be necessary for the differentiating activity of antimalarial quinolines [76].

Breast MCF-7 cells (wild-type for p53) presented 74% of cell cycle arrest in the G_1 phase after 24 h and 72 h of exposure to chloroquine 50 μM and everolimus [20 nM, 40-*O*-(2-hydroxyethyl)-rapamycin, an mTOR inhibitor], showing additive inhibitory effects when both drugs were added in 3-D cocultures. This proliferative reduction was confirmed by DNA quantification and increased levels of p53 and $p21^{Cip1}$ after the treatment of MCF-7 cells with chloroquine, but not everolimus, which indicates that G_1 arrest is mediated by tumor suppressor pathways p53 and p21 [48].

Loehberg et al. [46] detailed the dependency of p53 on the effects of chloroquine on BALB/c p53-null mammary epithelium cells and human mammary gland epithelial MCF10A line. Chloroquine-dependent DNA damage activates p53 and its downstream gene p21, resulting in the G_1 cell cycle arrest after a post-translation p53 activation by chloroquine-induced phosphorylation of ATM proteins, proving the existence of ATM-dependent phosphorylation of the p53 checkpoint (Figure 2). These molecular findings may explain the particular ability of chloroquine 3.5 mg/kg to reduce the growth rate and tumor incidence by 41% only in p53-wild-type BALB/c mice exposed to *N*-methyl-*N*-nitrosourea after 8 weeks of treatment. Since the TP53 is a mediator of hormone (estrogen/progesterone)-induced protection against chemical mammary carcinogenesis and no protection was observed in BALB/c p53-null mammary epithelium, it certainly shows that chloroquine can prevent breast cancer similar to estrogen/progesterone treatment and shows a p53 dependence [46].

As described before, autophagy is required for efficient growth of cells, and upon starvation chloroquine decreases LC3II lysosomal degradation [66, 73, 78, 79]. Therefore, 67-NR and 4-T1 mouse breast cell lines treated with chloroquine were sensitized preferentially in response to phosphoinositide 3-kinases or mTOR inhibitors, the route that directly regulates autophagy (Figure 3). Surprisingly, chloroquine sensitized 4-T1 and 67-NR cells to inhibit phosphoinositide 3-kinases or rapamycin even in *Atg12* gene nonfunctional cells, and the pan-caspase inhibitor zVAD-fmk (zVAD) did not increase cell survival, indicating that chloroquine should be able to sensitize even when autophagy has already been previously obstructed. Corroborating these findings, decreasing the cell viability involves a caspase-independent mechanism in which chloroquine but not bafilomycin A1 sensitizes cells to rapamycin-mediated cytotoxic actions, even though both of them block autophagy and LC3-II degradation [53].

2.2.5. Lung Cancers. Low concentrations of chloroquine (0.25–32 μM) up to 24 h exposure induced apoptosis of adenocarcinoma lung A-549 cells and vacuolation with increased volume of acidic compartments, but caused necrosis at 48 h and higher concentrations, as demonstrated by lactate dehydrogenase assays. Interestingly, in the presence of D609, a specific inhibitor of phosphatidylcholine-specific phospholipase C, only lower concentration effects were suppressed [80].

Hu et al. [50], using screening cytotoxic methods and absorbance assays, pointed out that the coculture of chloroquine and Akt inhibitors (phosphatidylinositol analogs, oligopeptides Akt-PH linkers, direct inhibitors of Akt-kinase activity, and blockers of catalytic subunit in the ATP-binding site) are more effective than either one alone. Such killing effects of chloroquine-mediated chemosensitization occurs at low concentrations as 10–20 μM and present specificity up to 120-fold for killing cancer than normal cells [50]. These findings indicate that chloroquine might significantly increase the therapeutic effects of some PI3K-Akt inhibitors with minor action on immortalized normal mammary gland epithelium 184B5 cells. Probably, chloroquine-mediated chemosensitization is related to the ability to block the formation of digestive vesicles, as those activated by tephrosin on cells, a natural rotenoid that induces endocytosis and subsequent degradation of human epithelial tyrosine kinase (HER-1 and 2) receptors [81].

2.2.6. Melanomas. A screening chemical library of antimalarial drugs against melanomas showed the endoperoxide-based redox antimalarial artemisinin-class members as inducers of apoptosis, while metastatic melanoma cells (A375, G361, and LOX) displayed a specific vulnerability to artemisinin and semisynthetic artemisinin-derivatives and NOXA-dependent apoptosis [82], a proapoptotic member of the Bcl2 family. Such sensitivity was corroborated by the upregulation of cellular oxidative stress, phosphatidylserine externalization, and cleavage of procaspase-3 [82]. Next, amodiaquine-exposed A-375 and G361 melanoma cells exhibited the formation of multivesicular single membrane-enclosed structures with electron-dense inclusions (indicative of lysosomal expansion), impairment of mitochondrial transmembrane potential, and accumulation of LAMP1, p62/SQSTM1, α-synuclein, lipofuscin, and LC3-II at concentrations as low as 1 μM [57], all accumulating autophagic proteins as a consequence of blocked autophagic-lysosomal flux (Figure 3). Such a blockade revealed a similar pattern of impaired lysosomal acidification in response to the treatment with either bafilomycin A1, amodiaquine, and chloroquine from a mechanistic point of view.

Intriguingly, a comparative analysis performed in A375 melanoma cells showed higher antiproliferative activity of amodiaquine when compared to chloroquine, which was confirmed by array analysis, revealing the modulation of gene expression antagonizing cell cycle progression (upregulation of *CDKN1A* and downregulation of *E2F1*) and modulation of the genes *TP53*, *CDKN1A*, *E2F1*, *CCND1*, and phosphorylated RB1. On the other hand, chloroquine failed to alter protein levels of TP53, E2F1, CCND1, and HSPA1A in A375 cells, demonstrating that the chloroquine treatment was not associated with the induction of cell cycle arrest, a finding extremely different from amodiaquine-induced melanoma cell cycle obstruction in the *S* phase [57].

Previous studies had already indicated amodiaquine as a more potent antimalarial molecule than chloroquine, a property attributed to a tropism targeting the acidic food vacuole of the plasmodium parasite [83]. Amodiaquine is a lysosomotropic 4-aminoquinoline-based tertiary amine as well, but it has a 1,4-aminophenol-pharmacophoric substituent capable of forming an electrophilic quinoneimine-metabolite under intracellular conditions of oxidation. Then, this reactive intermediate induces covalent protein adductions [57] and may contribute to higher potency.

2.2.7. Retinal Pigment Epithelial Cells. 10–250 μM chloroquine produced a persistent reduction in mTOR activity and intracellular calcium in retinal ARPE-19 cells, leading to the nuclear translocation of transcriptional factors for lysosomal biogenesis, expansion of lysosomes, severe suppression of autophagosome-lysosome fusion, and increased cytosolic levels of LAMP1, beclin-1, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and phospholipid intracellular content in 25-fold or greater [40, 84].

The inhibitors of endocytosis reduce endosomes and arrest a considerable amount of GAPDH into lysosomal cytosolic vesicles and cell membranes. On the other hand, its degradation is physiologically reduced or blocked as an adaptive reaction of lysosomes to retrieve normal functions, although accumulation of intracellular substrates, including p62, GAPDH, and phospholipids, are not entirely reestablished [84]. Anyway, chloroquine-induced protein accumulation indicates autophagy inhibition because p62 and GAPDH are degraded by lysosomes via autophagy and chaperon-mediated autophagy pathways, respectively [85].

GAPDH, an enzymatic 144-kDa tetramer expressed on the cell surface and secreted from cells leading to forward trafficking of active GAPDH out of cells, actively contributes to endosomal recruitment [85]. The versatility and promiscuity of functions and its interaction with multiple protein partners make GAPDH a vital tool for cell survival because it works as a scavenger agent to flush out misfolded molecules and activates inside processes during membrane trafficking and production of secretory lysosomes [86].

2.2.8. Mouse Embryonic Fibroblasts. In mouse embryonic fibroblasts (MEF), chloroquine and hydroxychloroquine confirmed their capacity to block autophagy in a concentration-dependent manner [87]. Indeed, $Bax^{-/-}$ and $Bak^{-/-}$ MEF cells were resistant against hydroxychloroquine-induced mitochondrial and plasma membrane permeabilization and hydroxychloroquine induced cathepsin B intracellular redistribution (Figure 3); besides, it was unable to cause mitochondrial depolarization, release of cytochrome *c*, or cell death when compared to wild-type MEF cells. Altogether, these data imply a specific sequence of subcellular alterations: (a) lysosomal accumulation resulting in the selective loss of mitochondrial potential and release of lysosomal enzymes, such as cathepsin B; (b) activation of Bax and mitochondrial permeabilization, and (c) caspase-3 activation, phosphatidylserine exposure, chromatin condensation, DNA loss, and apoptosis (Figure 2) [36]. Correspondingly, *in vivo* effects following 24 h or 48 h exposure of C57BL/6JOlaHsd mice to hydroxychloroquine 60 mg/kg showed Golgi changes and accumulation of LC3 [87].

These cells were also tested with a panel of approved-FDA drugs containing either quinoline or quinolone pharmacophores. Chloroquine caused the secretion of prostate apoptosis response-4 (Par-4) from wild-type p53 MEFs (Figure 2), as well as from normal human prostate stromal and lung fibroblast cells and their respective aminoquinoline derivatives, and induced Par-4 systemic secretion in C57BL/6 mice in a dose of 50 mg/kg body weight, and in patients from a clinical trial against cancer prior to surgery taking hydroxychloroquine [88]. As predictable, chloroquine caused the accumulation of LC-3II and p62/SQSTM1, but drug-induced secretion of Par-4 was not inhibited by zVAD, and differences in p62 levels have not been noticed after the treatment with wild-type Par-4 and $Par\text{-}4^{-/-}$ cells [88].

Par-4 is a tumor suppressor capable of inducing apoptosis selectively in most cancer cells without affecting normal/immortalized/nontransformed ones. The increase of Par-4 in the extracellular matrix causes cell death of tumor cells through binding to the overexpressing GRP78 receptor on the cell surface. Normal lines exhibit undetectable-to-low levels of this receptor [89], which protect them from the "friendly fire" though Par-4 is secreted by both normal and cancer tissues [89, 90]. Therefore, Par-4 secretion is not associated with apoptosis and does not affect autophagy in normal mouse embryonic fibroblasts. Meanwhile, the cocultures of chloroquine-treated $Par\text{-}4^{+/+}$ MEFs plus H-460 lung $p53^{+/+}$ and H-1299, HOP92, and KP-7B lung or prostate PC-3 $p53^{-/-}$ cancer cells were sensitive to apoptosis, but not when cocultured with chloroquine-treated $Par\text{-}4^{-/-}$ MEFs, and chloroquine failed to induce Par-4 secretion in prostate cancer cells (LNCaP, C42B, DU-145, and PC-3) and lung cancer cells (H-460 and A-549). These discoveries indicate that chloroquine-induced Par-4 secretion from normal lines causes paracrine apoptosis in cancer cells [86], and such action increases the selective expression of Par-4 receptor GRP78 on the surface of cancer cells [91] (Figure 2).

In vivo related findings in C57BL/6 mice bearing LLC1 pulmonary tumors also showed systemic elevation of Par-4 regressed tumor growth and metastatic lung nodules in animals treated with chloroquine 25 mg/kg/days for 5 consecutive days [88, 90]. Once again, the antiproliferative activity of chloroquine is linked to the activation of p53 and inhibition of NF-κB because these events promote Par-4 secretion [88] because p53 regulates classical components of the secretory route (Figure 2). This relatively unknown Par-4 pathway adds new importance to the traditional DNA protection roles of normal *TP53* gene to manage the tumor suppressor.

2.3. We Need to Think Outside the Box

2.3.1. New Pharmacological Judgement. Traditional comprehension about the effects of chloroquine and analogues on the lysosomal physiology implies a specific sequence of subcellular alterations: (a) lysosomal accumulation resulting in the selective release of lysosomal enzymes, such as

cathepsin B and D; (b) activation of Bax/Bad and mitochondrial permeabilization; (c) loss of mitochondrial potential, and (d) activation of caspases, phosphatidylserine exposure, chromatin condensation, DNA loss, and apoptosis (Figure 2).

However, new pharmacological judgements have arisen and changed some scientific dogmas in this area. Higher lysosomal pH was observed after 4 h of treatment with known alkalinizer drugs (fluoxetine, imipramine, dimebon, tamoxifen, chlorpromazine, amitriptyline, and verapamil), including chloroquine. Considering their high lipophilic structures (clogP ranging from 3.49 to 6.24), this suggests suitable entry into target cells including osteosarcoma U2OS, adenocarcinoma cervical HeLa, embryonic rat cardiomyocytes H9C2, and the human retinal pigment epithelial ARPE-19 line. Indeed, among amodiaquine, artemisinin, mefloquine, piperaquine, primaquine, quinacrine, and chloroquine, two antimalarial compounds (mefloquine and quinacrine) were about 30- and 60-fold more potent autophagy inhibitors on U2OS cells than chloroquine, respectively [92].

However, higher pH values were sustained no more than the compound exposure time, and after 24 h, renewed acidic organelles with pH between 4-5 were detected, indicating restorage of pH, which was also confirmed by nuclear translocation of transcription factors involved in lysosomal biogenesis, bigger lysosomal volume, and returning of cathepsin levels in order to reestablish optimal conditions for enzyme digestion [84, 93, 94].

Most studies have also suggested that chloroquine- or hydroxychloroquine-induced cell death is initiated by the "type II programmed autophagic/lysosomal pathway," including sequestration of organelles into autophagosomes and cytoplasmic vacuolization (Figure 3), and these processes are followed by later signs of the "type I programmed death" [36, 40, 66], which traditionally display karyorrhexis, DNA fragmentation, release of mitochondrial cytochrome *c*, activation of Bcl-2 proapoptotic proteins and caspases, cellular shrinkage, and phosphatidylserine externalization (Figure 2). Additionally, although members of the 4-aminoquinoline family, including chloroquine, hydroxychloroquine, and Lys-05 (dimeric chloroquine) inhibit autophagy [68], it has been suggested that ribosome biogenesis stress found in treated cells is not a general consequence of autophagy inhibition and that amodiaquine stands out among the 4-aminoquinoline family as a compound functioning by 2 independent mechanisms in two distinct intracellular environments: cytoplasm, where autophagy inhibition occurs and nucleolus, for diminution/blockage of ribosome biogenesis [49], which demonstrate that amodiaquine but not chloroquine inhibits ribosome biogenesis, disrupts nucleolar structure, and triggers degradation of RNA polymerase I.

As endosomal trafficking, endosome-lysosome fusion, membrane stability, signaling pathways, and transcriptional activity are impaired by hydroxychloroquine and chloroquine, it was hypothesized that combining them with radiation would be a good adjuvant alternative [47]. Nevertheless, chloroquine sensitization of some breast cancer lines revealed to be independent of autophagy inhibition, since sensitization was not mimicked by the knockdown of *Atg12* or *Beclin 1* genes or following treatment with bafilomycin A1, and chloroquine-induced cell death occurred even in the absence of Atg12 [53], proposing that reducing autophagy does not affect drug cytotoxicity ubiquitously in all human cells. Meanwhile, studies have demonstrated that chloroquine has specific cell sensitization effects to particular antimitotic drugs, whereas primaquine and mefloquine can sensitize resistant cancer cells to all antimitotic drugs without preference [81].

In a similar way, most investigations indicate that chloroquine does not block all forms and steps of the endolysosomal system. Analysis showed that chloroquine/hydroxychloroquine inhibits autophagy in initial phases, causing accumulation of acidic vesicular organelles and break/discontinue autophagosome-lysosome fusions, but they do not alter the ability of lysosomes to digest target macromolecules as conventionally accepted. In another point of view, compounds that simply increase the upstream autophagic flux without altering downstream fusion and degradation steps may not provide therapeutic benefit [95]. This would explain why only chloroquine and hydroxychloroquine are officially recommended as autophagy inhibitors by the Food and Drug Administration (FDA).

If we recall a more integrated concept, considering the well-established details about the blockage of autophagic flux and the capacity to inhibit PI3K/Akt/mTOR pathways and trigger ATM/ATR/p53/p21 signaling, it is possible to visualize that they complement themselves to cause death of cancer cells. Once mTOR is commonly phosphorylated at position 2448 via the PI3K/Akt and has been inhibited when higher levels of $p15^{INK4B}$, $p16^{INK4A}$, $p21^{Cip1}$, $p27^{Kip1}$, p53, and other suppressor tumors are present under stress conditions, p21 obliges G_1 restriction by inhibitory binding to CDK2/cyclin E or other CDK/cyclin complexes [45]. These physiological aspects support the theory that chloroquine or hydroxychloroquine exhibits, at least in part, antineoplastic effects altering the phosphorylation status of EGFR/PI3K/Akt/mTOR/Atg and p53 pathways [43, 46, 48, 49, 57] due to the direct inhibition of PI3K-Akt kinases, obstruction of catalytic subunits in the ATP-binding site [80], and/or misregulation of signaling of epithelial growth factor receptors (EGFRs) during endocytosis because they seem to weaken receptor-mediated endocytic transfers of TKRs to degradative compartments [95] (Figure 3).

In this context, the inhibition of tyrosine kinase receptors and downstream pathways (Receptor/PI3K/Akt or Receptor/Grb2/Ras/Raf/MEK/ERK) are examples of suitable targets to select antitumor repurposing molecules [50, 80, 81] (Figure 3). Despite that tyrosine kinase inhibitors have demonstrated enhanced selectivity, extra effects on some kinases and beyond their target family show intrinsic polypharmacology often favorable for clinical efficacy [6]. Therefore, blocking the signaling pathways that maintain the stemness is thus a rational goal to avoid recurrence as well as to block tumor growth and metastasis. Metastatic cancer or surgically nonresectable tumors show five years mortality above 90% in aggressive cancers, e.g., pancreatic tumors and

acute myeloid leukemia. Hence, with a few exceptions, survival rates of aggressive cancer types are low, mainly due to therapeutic failure [15].

Instinctively, these new studies indicate that chloroquine does not increase lysosomal alkalinization in all cell types in a similar magnitude, and lysosomes may even maintain their competence (completely or not) to digest organic material, confirming that chloroquine inhibits the fusion between autophagosomes and lysosomes in a concentration-dependent way, but it does not change the lysosomal activity considerably [84, 87]. The extent of increase in lysosomal pH and how much time lysosomes demand to normalize after compound exposure can diverge a lot if we take into consideration cell specificities, doubling time, phagocyte capacity, and how efficiently the cells/lysosomes respond to the compound sequestration. In a cell point of view, autophagy responses constitute stress adaptation that can suppress apoptosis, but when autophagy is blocked either at earlier or later stages, it may lead to apoptosis as a result of the failure for adaptation to environmental changed states.

Overall, the precise mechanism by which quinines sensitizes cancer cells by PI3K-Akt or MEK/ERK inhibitors is unclear, but it is recognized that such signal pathways are overexpressed or upregulated in cancer rather than in normal cells, which opens a “window of opportunities” to design more target drugs and clinical trials based on the lysosomal blockade ability. It is very important to remember that patients with metastases present tumors with multiple molecular and cellular characteristics. Therefore, the heterogeneity of metastases, tumor advance, and cell selection becomes a common problem observed in tumor resistance during the first line chemotherapies [6]. Therefore, including sensitizers with antimutagenic action (such as chloroquine) reduces the extent of primary DNA rearrangements responsible for the appearance of mutant clones and may delay/inhibit tumor progression.

A generalized overview also emphasizes the most vulnerable issue: do the effects of aminoquinolines share a common mode of action or are they the products of a variety of distinct processes? Once their mechanisms remain uncertain, molecular and clinical lessons are indispensable to detail dose/concentration-response relationships and safety-related aspects to guide the development of new modulating autophagy therapies [30].

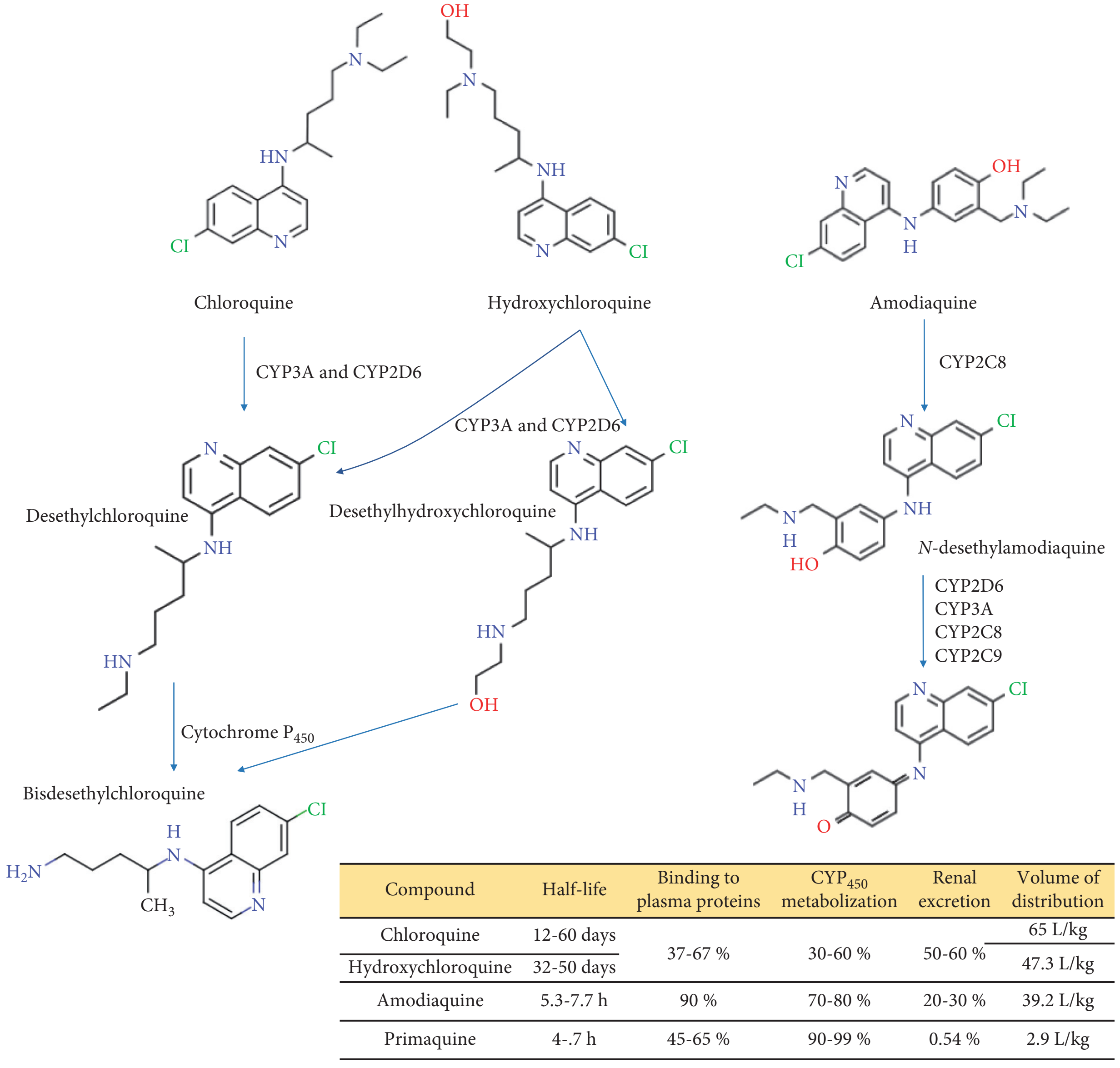
2.3.2. Pharmacokinetic-Related Toxicity. The most common adverse effects of chloroquine, hydroxychloroquine, amodiaquine, and other aminoquinolines in clinical use are nausea, abdominal/hypochondrial pain, changes in visual acuity (blurred vision), bitter taste in mouth, insomnia, weakness, arthralgia, back pain, pruritus (sensation of itching and stinging), diarrhea, and pale stools. Indeed, up to 50% of patients receiving hydroxychloroquine report some gastrointestinal effects. This is dose-dependent and most often occurs with loading doses >800 mg [96, 97], but 400–800 mg daily doses have been related to symptoms of psychosis, agitation, insomnia, confusion, hallucinations, paranoia, depression, catatonia, and suicides. These psychological/neurological effects may appear at any age, during acute or chronic use, and in patients with or without a history of psychiatric illness [98].

Poisoning with antimalarial drugs have also caused cardiovascular problems such as myocarditis, ventricular arrhythmias, cardiac arrest, and QTc prolongation due to the blockade of hERG potassium channels. Thereof, chloroquine, hydroxychloroquine, amodiaquine, and other derivatives should be used with caution in oncologic patients with cardiac diseases, history of ventricular arrhythmias, hypokalemia and/or hypomagnesemia, or bradycardia (<50 bpm), and during concomitant administration of QT interval prolonging agents (e.g., macrolides and fluoroquinolones) [9, 99–101]. If cardiotoxicity is suspected, quick discontinuation of the QT interval prolonging agents may prevent life-threatening complications.

Severe hypoglycemia with the loss of consciousness in patients treated or not with antidiabetic medications have been observed [102], inspite of beneficial effects for the metabolic syndrome [103]. Therefore, patients presenting clinical symptoms of hypoglycemia during treatment should have their blood glucose checked and treatment reviewed when necessary. Additionally, rhabdomyolysis [99] and ototoxicity when they are used by pregnant women in the 3rd trimester and even irreversible deafness [104] were reported. Nonetheless, health guidelines have indicated the maintenance of treatment with hydroxychloroquine during pregnancy and breastfeeding in patients with autoimmune diseases since these aminoquinolines do not cross the placenta easily and low quantity is found in breast milk [105].

Chloroquine and hydroxychloroquine structures and modes of action are closely similar except for an additional hydroxyl moiety, which makes hydroxychloroquine less permeable to blood-retinal barrier, and it allows faster clearance from retinal pigment cell, suggesting minor risks and safer option since long-term clinical trials with hydroxychloroquine tolerates higher daily doses and revealed less drug-drug interactions [102]. Their therapeutic window is relatively narrow, and retinal damage is one of the most common side effects for long term use [106]. Around 20% of chloroquine users showed ocular injuries due to high doses and treatment frequency in 1980s [39], and, since 1974, it has been a prescribed medicine in Japan due to chloroquine-associated retinopathy [107]. Thus, ocular or color vision examinations of patients under antimalarial therapies is indispensable for the early detection of retinal toxicity at a stage in which it is still reversible once treatment is interrupted [39]. The initial development of retinal damages with a daily dose of 800 to 1200 mg of hydroxychloroquine has been detected using sensitive retinal screening tests [108].

The simultaneous use of tamoxifen—the most prescribed selective modulator of estrogen receptors to treat hormone-receptor-positive, early/advanced-stage or metastatic breast cancers after surgery to reduce the risk of recurring—with hydroxychloroquine increases the risk of eye toxicity owing to the synergistic block of lysosomal/autophagy steps in retinal epithelial cells and accumulation of potentially toxic ubiquitinated proteins [108]. Although retinopathy is more



Compound	Half-life	Binding to plasma proteins	CYP_{450} metabolization	Renal excretion	Volume of distribution
Chloroquine	12-60 days	37-67 %	30-60 %	50-60 %	65 L/kg
Hydroxychloroquine	32-50 days				47.3 L/kg
Amodiaquine	5.3-7.7 h	90 %	70-80 %	20-30 %	39.2 L/kg
Primaquine	4-.7 h	45-65 %	90-99 %	0.54 %	2.9 L/kg

Figure 4: Metabolism of some aminoquinolines and pharmacokinetic features.

commonly correlated with chloroquine than with hydroxychloroquine, which might also be explained by the lower volume of distribution (Vd) for hydroxychloroquine (47.3 L) compared with chloroquine (65 L) (Figure 4). Ophthalmology guidelines have recommended comedication of tamoxifen plus hydroxychloroquine for up to 6 months, and a maximal daily dose of 5 mg/kg/day body weight of hydroxychloroquine not more than 5 years [30, 40, 106, 109].

Besides molecular similarities, chloroquine and hydroxychloroquine occur as enantiomers (R and S isomers), and *in vitro* and *in vivo* analyses have not shown important differences owing to the bioactivity [30], stereoselectivity of drug-drug interactions, and clinical consequences on toxicity due to the preferential metabolism of one enantiomer [105]. Both S(+)-chloroquine and -hydroxychloroquine present higher binding to albumin and α_1-acid glycoprotein, but hydroxychloroquine was enantioselective *in vivo* and in healthy volunteers, indicating the less protein-bound R(−)-enantiomer [110]. Then, the hydroxychloroquine binding degree to plasma proteins seems to control its distribution into cells, which can help explain how chloroquine have a larger Vd, since its R(−)-enantiomer is almost 2-fold less protein bound than the S(+)-enantiomer [105]. Notably, the S(+)-form of hydroxychloroquine is less taken up by rabbit ocular tissues [111], which suggests that the administration of the pure S(+)-enantiomer could offer better efficacy and lesser toxicity [105].

Experimental blockers such as 3-MA, bafilomycin A1, and short hairpin RNA (shRNA) knockdown of gene *Beclin* cause the deficiency of autophagy and increase tubular cell p53-dependent apoptosis during cisplatin treatment in kidney proximal tubular cells [112], supporting convincing

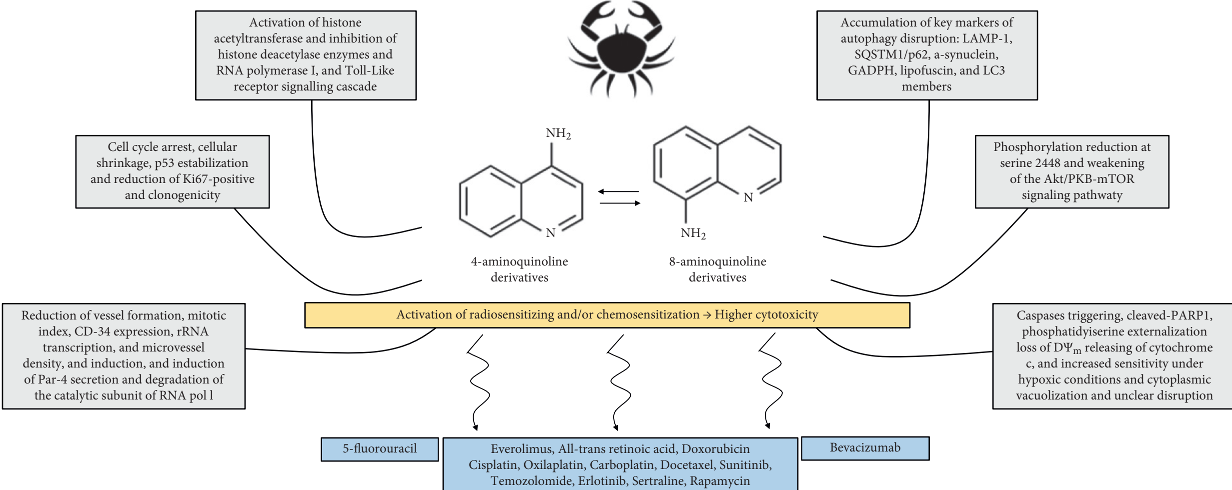


Figure 5: General properties of aminoquinolines on tumors.

data that autophagy is critical for renal cell survival. Hence, the concomitant exposure to anticancer agents and clinically available autophagy blockers (e.g., amodiaquine, primaquine, and analogues) also sensitizes normal tissues and can dramatically worsen renal function in patients with acute or chronic kidney illnesses. Under these circumstances, an impaired renal function increases the bioavailability of antimalarial drugs and comedications and the risk of adverse effects by pharmacological interactions.

In the pharmacokinetic context: (i) a single oral dose of chloroquine 300 mg can be detected in blood and urine from healthy volunteers up to 52 and 119 days postdose, respectively [113]; (ii) terminal elimination half-life of chloroquine, hydroxychloroquine, and their active metabolites (desethylchloroquine and desethylhydroxychloroquine, respectively, and finally, bisdesethyl chloroquine as a downstream metabolite of both drugs) varies from 20–60 days [30, 114]; (iii) both drugs can distribute to aqueous cellular and intercellular compartments, resulting in long mean residence times (about 1,300 h for hydroxychloroquine and 900 h for chloroquine) [114]; (iv) 30 to 50% of these antimalarial drugs are transformed by hepatic cytochromes P_{450}, mainly, CYP3A and CYP2D6 [115], and (v) about 37–67% of chloroquine/hydroxychloroquine bound to liver-derived plasma proteins [110, 116, 117]. Additionally, the half-life of amodiaquine is only 5.3–7.7 h, since it is subject to rapid first-pass metabolism and generate *N*-desethylamodiaquine, the principal route of disposition in humans, whose active metabolite has half-life >100 h and, therefore, amodiaquine can be considered a prodrug [118]. Thus, in contrast to amodiaquine, chloroquine and hydroxychloroquine are not highly bound to plasma proteins but have strong tissue binding.

It is also critical to ponder the coexistence of hepatic diseases (cancer-related or not), first pass metabolism, and comedications if the question is bioavailability or linked-side effects because elimination is significantly reduced in the presence of hepatic dysfunction, and nearly 50% of chloroquine is recovered in urine as unchanged drug. As background, a recent Brazilian study showed that the administration of hydroxychloroquine (400 mg twice daily for 7 days) without or with azithromycin (500 mg once a day for 7 days) caused a rise in liver-enzyme levels [119].

Indeed, clinical trials with anticancer purposes showed that adverse effects and toxicity of chloroquine and hydroxychloroquine are strongly dose-dependent (100–1200 mg/day). According to Common Terminology Criteria for Adverse Events version 3.0, toxicity was found with 100 to 200 mg/day [120–122]. Between 200 and 600 mg/day, the most common adverse effects were classified as grade 1 and 2, and include rash, visual blurring, sensitivity to light, nausea, diarrhea, fatigue, weight loss, vomiting, dyspepsia, anorexia, and dry skin [123–128]. The adverse effects of grade 3 or higher were detected from 600 to 1200 mg/day. Grade 4 toxicity was associated with myelosuppression at 800 mg/day of hydroxychloroquine [122]. Meanwhile, the combination of temsirolimus (25 mg/day, mTOR inhibitor) and hydroxychloroquine (200–1200 mg/day) was considered safe and tolerable, even at highest doses in patients with advanced solid tumors and melanoma [126]. Grade 2 or 3 adverse events were more common, resulting in a decrease of dosages after 2–3 months of treatment. Hydroxychloroquine and bortezomib, a proteasome inhibitor administered in patients with relapsed/refractory myeloma, cause grade 1 or 2 adverse events, mainly, but some patients experienced bone marrow suppression and grade 3 gastrointestinal toxicity [127]. At 1200 mg/day, hydroxychloroquine induced lymphopenia and an increase in serum alanine aminotransferase (grade 3/4) in patients with metastatic pancreatic cancer [128].

3. Conclusions

The mechanisms of sensitization attributed to aminoquinolines have a histological basis, but most of them are interconnected to the autophagic process. They express signals of autophagy disruption and cytotoxic-related action, including accumulation of key markers, predominantly,

LAMP1, p62/SQSTM1, LC3 members, GAPDH, beclin-1/Atg6, α-synuclein, and granules of lipofuscin.

Aminoquinolines act as lysosomal alkalinizers and take ownership during death-promoting mechanisms, which explain, at least in part, their chemotherapy and radiotherapy sensitizer effects when used as adjuvant option in clinical trials against solid tumors. They overturn lysosomal-related pathophysiological barriers, reduces uptake and drug distribution, avoid resistance, and improve cytotoxic activity response of weak-base clinical drugs, since they work as chemosensitizers under specific microenvironmental conditions, especially when acid lysosomal and inflamed tissues pH cause ion trapping and sequestering of chemotherapeutic drugs into protonated acidic endosomes. Additionally, they have also overwhelmed tumor resistance *in vivo*, suggesting that autophagy inhibition has antiangiogenic effectiveness as well. Therefore, in a mechanistic point of view, aminoquinolines induce ATM-ATR/p53/p21 signaling, caspase activation, and exhibit unspecific capacity for overlapping the apoptotic cascade to either upstream of caspase-3 activation and/or encompass nonp53/apoptotic/autophagy routes (Figure 5).

More specifically, two 4-aminoquinolines—chloroquine and hydroxychloroquine—accumulate slowly into cells and take time to develop cytotoxicity. Then, longer time exposure is believed to provide better antiproliferative effects, considering that they have a late onset but a prolonged action even after drug discontinuation. Moreover, no important differences have been found about the stereoselectivity of drug-drug interactions, clinical consequences on bioactivities, and additional pharmacokinetic-related toxicities. However, a continuous pharmacovigilance is required because these antimalarial molecules exhibit multiple cellular unspecific modes of action (undesired off-targets), relatively narrow therapeutic windows, recurrent adverse effects, and self-treatment-related poisoning. Retinopathy, mainly, has been more associated with chloroquine, and compromised renal and liver functions and increased the bioavailability of antimalarials and risk of adverse interactions. Therefore, their use must be under rigorous rules, ethical and medical prescription, and clinical and laboratory follow-ups.

Abbreviations

ATM-ATR: Ataxia telangiectasia-mutated/ataxia telangiectasia and Rad3-related kinases
Atg: Autophagy-related protein
CDK: Cyclin-dependent kinase
EGFR: Epithelial growth factor receptor
GAPDH: Glyceraldehyde 3-phosphate dehydrogenase
GRP78: Glucose regulated protein 78
LAMP1: Lysosomal associated membrane protein 1
MAPK: Mitogen-activated protein kinases, originally called ERK, extracellular signal-regulated kinases
LC3: Microtubule-associated protein 1A/1B-light chain 3
NF-κB: Factor nuclear kappa B
Par-4: Prostate apoptosis response-4
p53: Protein 53
p62: Protein 62
PARP1: Poly-(ADP-ribose)-polymerase 1
PI3K: Phosphatidylinositol 3-kinases
SQSTM1: Sequestosome 1
S6K1: p70S6 kinase1
TLR: Toll-like receptor
TKR: Tyrosine kinase receptor
UACA: Uveal autoantigen with coiled-coil domains and ankyrin repeats
Vps34: Vesicular protein sorting 34
4E-BP: 4E-binding protein
5-FU: 5-Fluorouracil
zVAD-fmk: Benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone.

Data Availability

The data used to support the findings of this study are cited as references.

Conflicts of Interest

The authors declare that they have no conflicts of financial interest or personal relationships that could influence this work and outcomes reported in this paper.

Authors' Contributions

PMPF planned the review and wrote about mechanisms of action and toxicokinetic findings. JROF collaborated in toxicity-related issues. DPB discussed about drug reuse with anticancer purposes. RWRS and GCGM analyzed *in vitro* mechanisms and revised the article. All authors have read and agreed to the published version of the manuscript.

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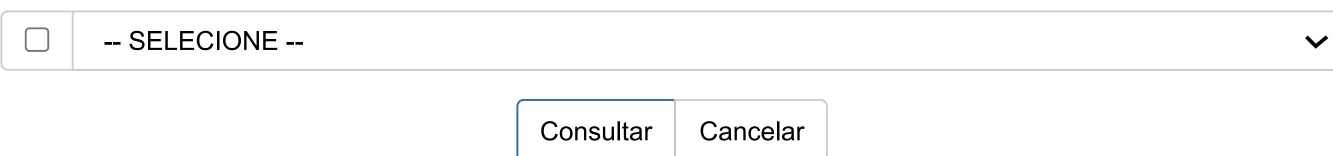

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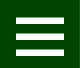

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Performance of Eucalyptus clone AEC144 inoculated with diazotrophic bacteria in the Southwest of Bahia

Vitor Alves Monteiro da Silva ; Joilson Silva Ferreira; Rayka Kristian Alves Santos; Carol Chaves Nascimento; Vinicius Alves Rodrigues ; Maida Cynthia Duca de Lima

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Development of muffin with the incorporation of olive pomace flour, extra virgin olive oil and hydrolyzed soy protein

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The importance of seedling production for urban afforestation: public nurseries in the city of Teresina, Piauí, Brazil

Lorran André Moraes; Tainara Lima de Sousa Passos ; Leilson Alves dos Santos; Adriana de Sousa Lima ; Waldiléia Ferreira de Melo Batista ; Kelly Polyana Pereira Santos; Roselis Ribeiro Barbosa Machado

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Dislane Batista Silva ; Georgia Maciel Dias de Moraes; Francisca Joyce Elmiro Timbó Andrade ; Herlene Greyce da Silveira Queiroz ; Mirla Dayanny Pinto Farias
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Effect of mulberry leaf extract (Morus nigra L.) on cardiovascular inflammatory process and insulin resistance of dyslipidemic mice

Carlos Roberto Pereira; Ana Luísa Cabral de Faria; Maria das Graças de Souza Carvalho; Brígida Monteiro Vilas Boas ; Erika Kristina Incerpi Garcia; Fabiana Lucio de Oliveira; Leandro dos Santos; Lais Roncato de Carvalho Alves; Aline Manke Nachtigall; Flávia Helena Pereira; José Antônio Dias Garcia
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Liliane Andrade da Silva; Annie Evelyn Souto Raposo; José Honório Pereira Lopes Neto; Kléber de Sousa Oliveira; Evandro Leite Souza; Octávio Luiz Franco; Haíssa Roberta Cardarelli
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Water management for housing located in rural areas: case study

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Gastrointestinal parasites in non-human primates from the Wildlife Animal Screening Center of Vitória da Conquista, Bahia, Brazil

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Quality and postharvest shelf life of melon fruits subjected to different irrigation depths

Manoel Valnir Júnior; Vera Lúcia Antunes de Lima; Raimundo Rodrigues Gomes Filho; Clayton Moura de Carvalho; Sílvio Carlos Ribeiro Vieira Lima; João Paulo Alves da Rocha

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Descriptive analysis of the satisfaction of student users of the university restaurant, Universidade Federal Rural da Amazônia, Belém, Pará

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Influence of seed strength on bean response to phosphorus fertilization

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The SWOT matrix as analysis tool to subsidize the creating an intercity consortium on gestating and managing the Urban Solid Waste

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Use of chitosan in agriculture: a review with an emphasis on seed application

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Pathogenicity of Beauveria bassiana to Atta sexdens rubropilosa (Hymenoptera: Formicidae) in laboratory conditions

Elisângela de Souza Loureiro; Giovana Daniela Busarello; Luis Gustavo Amorim Pessoa; Manoel Araecio Uchoa-Fernandes; Tatiana Souza do Amaral; Marcelo Bruno Pessoa
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Assessment of the level of knowledge of prescription of nsaids for horses in northeastern brazil

Dinamérico de Alencar Santos Júnior; Caio Victor Damasceno Carvalho; Felipe Pires de Souza Bomfim; Matheus Teixeira Borges Pereira; Saulo de Almeida Carvalho; Eldinê Gomes de Miranda Neto; Pierre Barnabé Escodro
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Physiological quality of Physalis peruviana seeds under water stress conditions

Valmira Hoste Dutra; Livia Mara Araujo Amorim; Ana Maria Guimarães Bernardo; Ediane Conceição Alves; Cleber Macedo de Oliveira; Denise Cunha Fernandes dos Santos Dias
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Floristic composition in headwaters areas of the Piauitinga river Sub-Basin in Sergipe, Brazil

Crislaine Costa Calazans; Gilmara da Silva Freire; Ana Paula do Nascimento Prata; Robério Anastácio Ferreira
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Quality of watermelon fruits under different doses of nitrogen fertilization

Rodrigo Afonso dos Anjos; Mateus Aparecido Rodrigues Santos; Manoel Xavier de Oliveira Júnior; Francisco Valdevino Bezerra Neto; Alisson Macendo Amaral; Maria Ângela Cruz Macêdo dos Santos
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Effect of ethanolic extracts of plants on Spodoptera frugiperda (Lepdoptera: Noctuidae)

Janaína De Nadai Corassa; Monique Machiner; Dênia Mendes de Sousa Valladao; Carla Regina Andrighetti; Jaqueline Bilenki Weberling
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First report of fungal Sporothrix schenckii complex isolation from feline with possible zoonotic transmission in the city of Belém, Pará, Brazil: Case report

Barbara Wilka Leal Silva; Marcelino Antônio Costa Maués; Pedro Henrique Marques Barrozo; Jacqueline da Silva Brito; Caio Cezar Nogueira de Souza; Marcely Karen Santos do Rosário; Caroliny do Socorro Brito Santos; Alzira Alcantara Mendes Queiroz Neta; Fernanda Monik Silva Martins; Leonildo Bento Galiza da Silva; Lívia Medeiros Neves Casseb; Andréa Maria Góes Negrão; Mylenna de Cássia Neves Guimarães; Andrea Viana da Cruz; Alexandre do Rosário Casseb
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Detection of low molecular weight carbohydrates in different mango varieties at two stages of maturation

Klelma Teixeira da Cunha; Taynara de Sousa Rego Mendes; Charllyton Luís Sena da Costa
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Case study on the clinical and anatomopathological descriptions of dog with primary uveal lymphoma

Fernanda Gosuen Gonçalves Dias; Larissa Fernandes Magalhães; Lucas de Freitas Pereira; Cristiane dos Santos Honsho; Marina Laudares Costa; Alex Roberto de Oliveira; Daniela do Nascimento Belmiro; Victória Marques Russo Ramos; Adriana Torrecilhas Jorge
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Use of phonolite and potassium-solubilizing bacteria in bean crops

Sérgio Diogo de Pádua; Ligiane Aparecida Florentino
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Production of biosurfactants by Mucoralean fungi isolated from Caatinga bioma soil using industrial waste as renewable substrates

Thayná Rhomana da Silva Cândido; Rafael de Souza Mendonça ; Uiara Maria de Barros Lira Lins; Adriana Ferreira de Souza; Dayana Montero Rodriguez; Galba Maria de Campos-Takaki; Rosileide Fontenele da Silva Andrade
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Pathogenicity of Beauveria bassiana strains against Drosophila suzukii (Diptera: Drosophilidae)

Jason Lee Furuie; Andressa Katiski da Costa Stuart; Franciele Baja; Morgana Ferreira Voidaleski; Maria Aparecida Cassilha Zawadneak; Ida Chapaval Pimentel

e41611225730

Intellectual property of fruit and vegetable cultivars in Brazil

Leila Moura Soares Nunes; Ana Karla de Souza Abud

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Intensive rearing in confinement as a management strategy in beef cattle - literature review

Igor José Carvalho Batistelli; Juliana Carla de Oliveira Rodrigues Batistelli; Bruno Luiz Bess; Flávio Luiz de Menezes; Kamila Andreatta Kling de Moraes; Eduardo Henrique Bevitori Kling de Moraes

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Direct cost method applied to calculate milk production costs

José Leoncio Delmondes Pereira Freitas; Evandro Neves Muniz; Anselmo Domingos Ferreira Santos; Sônia Magna Moura Delmondes Freitas ; Luana Moura Delmondes Freitas; Valdir Ribeiro Junior; Leda Maria Delmontes Freitas Trindade; Gladston Rafael de Arruda Santos; Camilla Mendonça Silva

e2911225328

Path analysis of phosphorus content in different irrigated corn constituents

Reginaldo Miranda de Oliveira; Rubens Alves de Oliveira; Tulio Russino Castro; Margareth Evangelista Botelho; Raquel Dias Rodrigues; Gloria Milena Rojas Plazas; Tayssa Menezes Franco; Job Oliveira

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Pemphigus foliaceus in a dog – Clinical, cytopathological and histopathological relation

Péter de Lima Wachholz; Eduarda Santos Bierhals; Guilherme Ferreira Robaldo; Rosimeri Zamboni; Josiane Bonel; Raqueli Teresinha França; Mariana Cristina Hoeppner Rondelli

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Comparative study of the partial replacement of Triticum durum semolina in fettuccine pasta by bamboo fiber and young bamboo culm flour

Amanda Rios Ferreira; Mária Herminia Ferrari Felisberto; Elisa Cristina Andrade Neves; Jorge Herman Behrens; Maria Teresa Pedrosa Silva Clerici

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Dermatophytosis by Trichophyton verrucosum in domestic feline – case report

Danilo Rocha de Melo; Juliany Nunes dos Santos; Evelyn Carla da Frota Rocha; Angélica Prado de Oliveira ; Jôiciglecia Pereira dos Santos; Valesca Ferreira Machado de Souza; Valquíria Tatiele da Silva Rodrigues; Layze Cilmara Alves da Silva Vieira

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Influence of fertigation with wastewater on the soil and growth of tree seedlings

Lucas Rafael Sanches; Robson Fernando Missio; Juliano Cordeiro

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Quality of 'Ponkan' mandarin fruits using alternative coatings and application of UV-C radiation

Camila Schwartz Dias; Mariana Larrondo Bicca; Flávia Loureço da Silva; Tâmara Foster Acosta; Gabrielle Leivas; Paulo Celso Mello Farias; Vagner Brasil Costa; Flávio Gilberto Herter

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Outbreak due to Fusarium solani on a Brazilian ostrich farm

Henri Donnarumma Levy Bentubo; Vivian Ferreira da Silva; Maria Bárbara Baptista Capellos Daruiz Mangiaterra; Sarah Santos Gonçalves

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Evaluation of the hematological and biochemical profiles of Giant Anteaters (Myrmecophaga tridactyla) with severe thermal burns: Report of six cases

Tayane Bruna Soares Magalhães; Adriane Jorge Mendonça; Carolina Zorzo; Thaís Oliveira Morgado; Sandra Helena Ramiro Corrêa; Ana Letícia Prata Palemo; Emily Raquel da Silva Nardes; Kerilen Silva Costa

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Evaluation of enzymatic production of hydrolases and oxyredutases by Fusarium pseudocircinatum and Corynespora torulosa isolated from caesarweed (Urena lobata L., 1753)

Sarah Raquel Silveira da Silva Santiago; Paulo Alexandre Lima Santiago; Marta Rodrigues de Oliveira; Rafael de Souza Rodrigues; Anderson Nogueira Barbosa; Gilvan Ferreira da Silva; Jeferson Chagas da Cruz; Afonso Duarte Leão de Souza; Antonia Queiroz Lima de Souza

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Antibacterial activity of Kombucha against Escherichia coli and Staphylococcus aureus and Minas Frescal cheese production with Scoby

Eduardo Bergamaski Coelho; Bruna Barnei Saraiva; Bruna Moura Rodrigues; Ranulfo Combuca da Silva Júnior; Katieli da Silva Souza Campanholi; Dayse Maria Bernardo Maricato; Paula Matumoto Pintro; Magali Soares dos Santos Pozza

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Parasitological diagnosis of Bovine Parasitic Sadness in Bahia - Retrospective study from 2017 to 2021

Regiane Pereira Benevides Silva; Leonardo Ribas Pacheco; Tiago Silva Lima; Raquel Moreira Oliveira; Melyssa Silva Souza; Cristiane de Jesus Barbosa; Jorge Raimundo Lins Ribas; Luciana Veiga Barbosa

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Analysis of the influence of the media on the decisions of the Jury Court

Rosana Santos de Almeida; Jonatas Claudio Farias Maciel; Raquel Formiga de Medeiros; Hugo Sarmento Gadelha; Hiran Mendes Castro Filho; Suzana Araújo dos Santos; Marcela da Silva Varejão; Agílio Tomaz Marques

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Ferns and lycophytes from Rancho Souza, municipality of Abaetetuba, Pará State, Brazil

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Wetlands in Brazil: classification, floristic composition and biological Nitrogen fixation

Ana Beatriz Carvalho Terra; Ligiane Aparecida Florentino; Paulo Roberto Landgraf

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Effect of commercial product worth orange oil base on application quality

Wendson Soares da Silva Cavalcante; Nelmício Furtado da Silva; Marconi Batista Teixeira; Giacomo Zanotto Neto; Estevão Rodrigues; Fernando Rodrigues Cabral Filho; Fernando Rezende Corrêa

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Fernando Nogueira
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Review of three medicinal and ornamental species of the family Apocynaceae Juss.

Allyson Francisco dos Santos; Luciano Temoteo dos Santos; Marcio Pereira do Nascimento; Elias Laurindo de Oliveira; Talina Guedes Ribeiro; Francisco Diego Pereira; Geralda de Araújo Lima; Willyan Tavares Gonçalves; Maria Ivaneide Rocha; Tânia Kelly Mendes Feitosa; Mariana Ferreira da Cruz; Suzana Gonçalves Santana Tavares; Maria Eliana Vieira Figueroa; Ginna Gonçalves Pereira
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Chemical, biological, and pharmacological evaluation of the aqueous extract of Ilex paraguariensis, St. Hill. (Aquifoliaceae)

Andressa Flores Santos; Elberth Manfron Schiefer; Mônica Surek; Cleverson Antônio Ferreira Martins; Paulo Roberto Worfel; Guilherme Lanzi Sassaki; Lauro Mera de Souza; Luciana Cristina Nowacki; Wesley Mauricio de Souza

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Evaluation of the traditional use and commerce of medicinal plants and phythoterapics in the municipality of Resende, RJ: A contribution to the development of the National Policy on Medicinal Plants and Phythoterapics in Sul Fluminense

Amanda Candido Custódio ; Gabriela de Paula dos Santos Caetano; Márcia Rosa de Almeida

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Evaluation of Endodontic Productivity in Oral Public Healthcare Services in Minas Gerais, Brazil

José Leonardo Barbosa Melgaço-Costa; Renata Castro Martins; Efigenia Ferreira Ferreira; Antonio Paulino Ribeiro-Sobrinho

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Global Burden of Disease: Estimate and time trend of the burden of leprosy in the state of Alagoas, Brazil from 2001 to 2019

Jackson Silva da Cabral; Dalton Ferreira Matos; Letícia Pereira Bezerra; Rosália Elen Santos Ramos; Maria Letícia Pereira Aquino; Quezia Machado dos Santos Araújo; Robert Lincoln Barros Melo; Éverton Santana Freire; Wandklebson Silva da Paz; Delma Holanda de Almeida

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Bárbara Nascimento Santana; João Batista Cavalcante Filho; Marco Antonio Prado Nunes

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The mandibular rehabilitation multidisciplinary after mandibulectomy

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Use of platelet- and leukocyte-rich fibrin (L-PRF) as an alternative for tissue regeneration in sinus lift surgery

Mauro Wilker Cruz de Azevedo ; Lucas Andeilson dos Santos Matos; Tharlles Bruno Lima Silva; Wállyson Alves e Silva; Fabielly Camelo do Nascimento; Thaís Monte Silva; Laís Pereira Leal; Leyriane Mendes Paiva; Jandenilson Alves Brígido

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Laura Marcela Teotonio Magalhães; Ana Kelly Carvalho Gomes; Vinicius Pacheco da Silva; Samir Mansour Moraes Casseb; Marinês da Costa Farias; Elizandra Carneiro Baía; Marli de Oliveira Almeida; Diogo de Matos Botelho; Milena Machado de Matos

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Use of Financial Emergency Aid for adults with type 1 diabetes during COVID-19 pandemic in Brazil, 2020

Aline Leão Reis; Aline Daniela da Cruz e Silva; Gabriela Correia Uliana; Talita Nogueira Berino; Manuela Maria de Lima Carvalhal; Jeane Lorena Dias Kikuchi; Daniela Lopes Gomes

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Analysis of the prevalence of von Hippel-Lindau Syndrome in patients with hemangioblastomas of the Central Nervous System

Gustavo Soares Gomes Barros Fonseca; Vivianne Maria Laranjeiras Monte Freire; Lais Lima Bonfim; Elana Cristina da Silva Penha; João Victor Araújo Guimarães; Raphael Erick Lima Pereira; Gabriel de Sousa Macedo; Filipe Augusto Lopes Cajubá de Britto; Letícia Muniz de Abreu Murad; Alessandra do Rosário Brito; Lara Letícia Teixeira Reis; Amanda Cordeiro Santos; Agostinho Rodrigues Mesquita Neto; Julianne Souza Prazeres; Luiza Mariana Batista Lima Cunha; Ana Vitória Feitosa Barroso Maia; Carolynne Weba da Silva; Fernando de Abreu Borges; Monaliza Brito de Almeida; Samantha Cunha Vieira; Isabela Coelho Brito Soares; Liciana Tapety Sá; Lucca Adriano Pereira; Thalita Martins Bezerra; Ivana Mota Soares; Rebeca Machado Castro Sousa; Maria Beatriz Celedonio Coelho; Felipe Ramos Caldeira

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Evaluation of prematurity in a Baby-Friendly hospital in the interior of Sergipe in 2019

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Apixification on immature tooth traumatized with crown-root fracture: case report

Thatiana Cristino Freire; Andréa Albuquerque Lima; Kaio Coura Melo Pacheco; Phillip Lucas Ricardo Pereira; Clovis Stephano Pereira Bueno; Daniel Pinto de Oliveira; Leopoldo Cosme Silva; Lais Christina Pontes Espíndola; Dyana dos Santos Fagundes

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Hospitalized patients profiles due to Cerebral Vascular Accident in a urgency and emergency unit in a hospital school in West Parana and the performance of the physical therapist in these cases

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Profile and physiotherapeutic intervention of patients victims of trauma admitted to the urgent and emergency unit of a University Hospital in West Paraná

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Comparison of inflammatory and thrombotic profiles of patients with COVID-19 in their different outcomes: hospital discharge and death

Monike Aparecida Matos de Oliveira; Izabella Brito de Souza; Juan Andrade Silva; Carolina Heitmann Mares Azevedo Ribeiro; Ana Cristina Lo Prete
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Antimicrobial activity of plant extracts of spices from northern Brazil

Ananda Emilly de Oliveira Brito; Carlena Sinara Martins da Silva
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Profile of notifications for cosmetics reported to Notivisa, Brazil

Marcela de Oliveira Ramos; Danilo de Oliveira Ramos; Zaida Maria Faria de Freitas; Mariana Sato de Souza Bustamante Monteiro; Márcia Maria Barros dos Passos
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Kethylen Barbara Barbosa Cardoso; Maria Clara Nascimento; Anna Carolina Batista; Vagne de Melo Oliveira; Thiago Pajeú Nascimento; Juanize Matias da Silva Batista; Romero Marcos Pedrosa Brandão Costa; Lorenzo Pastrana; Ana Lúcia Figueiredo Porto
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Protease with fibrinolytic and collagenolytic activity produced by Aspergillus ochraceus URM604

Kethylen Barbara Barbosa Cardoso; Thiago Pajeú Nascimento; Vagne de Melo Oliveira; Romero Marcos Pedrosa Brandão Costa; Lorenzo Pastrana; Juanize Matias da Silva Batista; Ana Lucia Figueiredo Porto
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Parendodontic surgery to remove a periapical cyst: case report

Rosana Maria Coelho Travassos; Éwerton Daniel Rocha Rodrigues; Camila Marques Zimmerle; Fernanda Raquel Cabral Campos Carvalho; Jade Rodrigues Monteiro; Thays de Souza Mendes; Marina Maria Ferreira Falcão; Maria Eduarda de Morais Cavalcanti

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Eating and sociodemographic data of adults with type 1 Diabetes mellitus during COVID-19's social distancing

Jullyana Vago de Vilhena; Heloisy Andrea da Costa Brasil; Jeane Lorena Dias Kikuchi; Manuela Maria de Lima Carvalhal; Daniela Lopes Gomes

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Alex Sander Lopes da Silva; Maria Luiza Silveira de Carvalho; Clicia Maria de Jesus Benevides

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Marlene Simões e Silva; Pamela Nery do Lago; Vinícius Martins Machado; Eliseu da Costa Campos; Samanntha Lara da Silva Torres Anaisse; Marta Luiza da Cruz; Tatiana Alves Costa; Adriana Simões Moreira Rocha; Andréa Paula Dourado Vasconcelos; Lívia Sayonara de Sousa Nascimento; Pedro Henrique Santos Oliveira; Eugênio Barros Bortoluzi; Renata Cavalcanti Cordeiro; Amanda Araújo Brandão; Ítallo Bernardo Souto

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Prevalence of histopathological findings of esophageal mucosa and their correlation with Helicobacter pylori

Gabrielle Barbosa Vasconcelos de Souza; Elomar Rezende Moura; Yasmin Tourinho Delmondes Trindade; Durval José de Santana Neto; Larissa Gonçalves Moreira; Gabriel Ponciano Santos de Carvalho; Íkaro Daniel de Carvalho Barreto; Décio Fragata da Silva; Luíse Meurer; Leda Maria Delmondes Freitas Trindade
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Prevalence of frailty in institutionalized elderly in the city of Rio Verde – Goiás

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Analysis of the correlation of soil physical attributes with maize grain yield components in different cultivation systems

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Guarana (Paullinia cupana Kunth), marapuama (Ptychopetalum olacoides Benth.), gentian (Gentiana lutea L.), quassia (Quassia amara L.) and their properties: a brief review

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Produtos alimentícios à base de extrato de Cannabis: do "Brisadeiro" à busca por efeito terapêutico

Food products based on Cannabis extract: from "Brisadeiro" to searching for a therapeutic effect

Productos alimenticios a base de extracto de Cannabis: del "Brisadeiro" a la búsqueda del efecto terapéutico

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Resumo

Introdução. Os produtos comestíveis à base de maconha tornaram-se um mercado lucrativo e de grande procura. Apesar de no Brasil não ser legalizada, a maconha é encontrada em preparações orais comercializadas ilegalmente no país e a busca por esses produtos tem crescido nos últimos anos. O presente estudo tem por finalidade reunir dados da literatura científica sobre a fisiologia do sistema endocanabinóide, efeitos do consumo de Cânabis por via oral, farmacocinética, possíveis efeitos tóxicos, terapêuticos e formas de detecção, buscando contribuir para o preenchimento da lacuna ainda existente sobre o tema. Metodologia. Foi realizada revisão integrativa na base de dados PubMed para publicações dos últimos 5 anos em português, inglês e espanhol. Resultados. A pesquisa resultou em 128 artigos os quais foram removidos os trabalhos que não preenchessem os critérios de inclusão, restando 28 artigos utilizados. Conclusões. É necessário que seja realizado um número maior de ensaios clínicos com canabis por via oral, nas diversas formulações existentes, para melhor compreender sua farmacocinética, farmacodinâmica, potencialidades terapêuticas e seus efeitos adversos.

Palavras-chave: Maconha; Canabinoides; Receptor de Canabinoide.

Abstract
Introduction. Cannabis-based edibles have become a lucrative and in-demand market. Despite not being legalized in Brazil, marijuana is found in oral preparations illegally marketed in the country and the search for these products has grown in recent years. The present study aims to gather data from the scientific literature on the physiology of the endocannabinoid system, effects of oral cannabis consumption, pharmacokinetics, possible toxic and therapeutic effects and ways of detection, seeking to contribute to filling the gap that still exists on the theme. Methodology. An integrative review was carried out in the PubMed database for publications of the last 5 years in Portuguese, English and Spanish. Results. The search resulted in 128 articles from which the works that did not meet the inclusion criteria were removed, leaving 28 articles used. Conclusions. It is necessary to carry out a greater number of clinical trials with oral cannabis, in the various existing formulations, to better understand its pharmacokinetics, pharmacodynamics, therapeutic potential and its adverse effects.
Keywords: Marihuana; Cannabinoids; Cannabinoid Receptor.

Resumen
Introducción. Los comestibles a base de cannabis se han convertido en un mercado lucrativo y en demanda. A pesar de no estar legalizada en Brasil, la marihuana se encuentra en preparaciones orales comercializadas ilegalmente en el país y la búsqueda de estos productos ha crecido en los últimos años. El presente estudio tiene como objetivo recopilar datos de la literatura científica sobre la fisiología del sistema endocannabinoide, efectos del consumo oral de cannabis, farmacocinética, posibles efectos tóxicos y terapéuticos y formas de detección, buscando contribuir a llenar el vacío que aún existe sobre el tema. Metodología. Se realizó una revisión integradora en la base de datos PubMed para publicaciones de los últimos 5 años en portugués, inglés y español. Resultados. La búsqueda resultó en 128 artículos de los cuales se eliminaron los trabajos que no cumplieron con los criterios de inclusión, quedando 28 artículos utilizados. Conclusiones. Es necesario realizar un mayor número de ensayos clínicos con cannabis oral, en las distintas formulaciones existentes, para conocer mejor su farmacocinética, farmacodinamia, potencial terapéutico y sus efectos adversos.
Palabras clave: Marihuana; Cannabinoides; Receptor de Cannabinoides.

1. Introdução

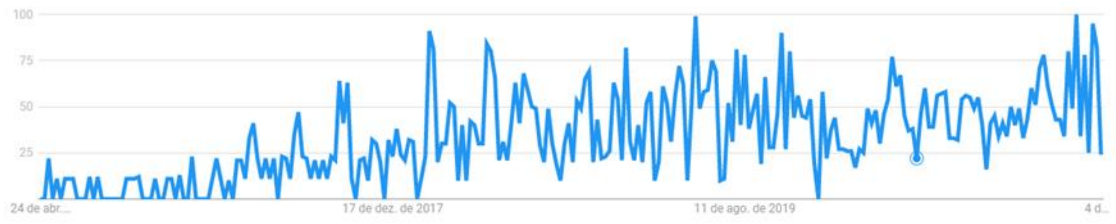
Produtos alimentícios com extratos de Cânabis surgiram como um mercado lucrativo em países onde o uso de maconha foi legalizado (White et al., 2020). A procura por esses produtos têm aumentado, uma vez que a curiosidade e o consumo de forma discreta, estimulam a procura (Barros et al, 2016; Boisvert et al., 2020). Além disso, há uma crença que estes sejam mais seguros, isto porque a Cânabis fumada é comparada ao cigarro e fumo comum, que apresentam toxicidade ao pulmão. Todavia, comestíveis com extratos de Cânabis podem ser tão perigosos quanto outras formas de consumo (Leventhal et al., 2020). Nesse sentido, o maior perigo é a lacuna de conhecimento que existe sobre os efeitos sistêmicos do consumo por via oral e formas de detecção (Farmer et al., 2019).

Em um recente estudo prospectivo de patentes de produtos alimentícios com extratos de Cannabis ou com Canabidiol, revelou um crescente aumento do registro de patentes, com a maioria ativa, sendo os maiores detentores países como: China, Estados Unidos e Canadá (Santos et al., 2021). Isto revela a importância do mercado, e que este precisa ser regulado.

Apesar de no Brasil não ser legalizada, é comum encontrar relatos da presença de maconha e/ou seu extrato em alimentos. Nesse sentido, surgi o “Brisadeiro” que é uma versão ilegal do famoso doce brasileiro o “Brigadeiro”. No Brisadeiro partes da Cânabis são previamente processadas e tostadas em forno, posteriormente sofrem uma extração a quente com manteiga. Essa manteiga “batizada” é utilizada no preparo do Brisadeiro e outros produtos alimentícios. É importante destacar que o procedimento de aquecimento é necessário para a descarboxilação do Tetra-hidrocanabinol, e, portanto, para a ativação de canabinóides e terpenos através do calor (Barrus et al., 2016).

Em consulta ao Google Trends®, que é uma ferramenta do Google capaz de verificar o quanto determinado termo está sendo pesquisado na internet, conforme Figura 1, a pesquisa pelo “Brisadeiro” tem crescido nos últimos cinco anos.

Figura 1: Termo de pesquisa "Brisadeiro", filtro aplicado: últimos 05 anos (2016 - 2021), ferramenta Google Trends®.



Fonte: Google Trends®.

Nesse contexto, o presente estudo tem por finalidade reunir dados da literatura científica sobre a fisiologia do sistema endocanabinóide, os efeitos do consumo de Cânabis por via oral, sua farmacodinâmica e farmacocinética. Bem como, dados clínicos importantes para a compreensão dos possíveis efeitos tóxicos, terapêuticos e formas de detecção, buscando contribuir para o preenchimento da lacuna de conhecimento existente.

2. Metodologia

Foi realizada uma revisão integrativa a partir da base de dados PubMed para publicações dos últimos 5 anos em português, inglês e espanhol. A coleta de dados foi realizada de março a setembro de 2021, com a combinação dos descritores ((Cannabis OR Cannabinoids) AND "Edibles"). Para garantir maior segurança a pesquisa, os descritores selecionados foram controlados por MESH. Definido os descritores, então foram determinados os critérios de inclusão e exclusão. Como critério de inclusão: I – Estudos empíricos, II – Língua inglesa, portuguesa ou espanhola, III- Artigos que buscam avaliar os efeitos de produtos alimentícios à base de extrato de Cannabis ou que analisam os efeitos do consumo por via oral. Enquanto os critérios de exclusão foram: I- Estudos experimentais com animais, II – Estudos *in vitro*, III – Estudos que abordem outra via de consumo que não seja a oral.

A pesquisa inicial resultou em 128 artigos, estes foram lidos os títulos e resumos disponíveis, sendo retirados 15 artigos por serem revisões e 47 por tratar de outra via que não a oral. Resultando em 66 artigos para leitura completa, destes 1 correspondia a estudos com animais, e 37 a outros assuntos como legislação e estudos de consumo. Restando 28 artigos que foram incluídos no presente trabalho para compor a síntese qualitativa desta revisão integrativa. A estratégia de busca pode ser visualizada na Figura 2.

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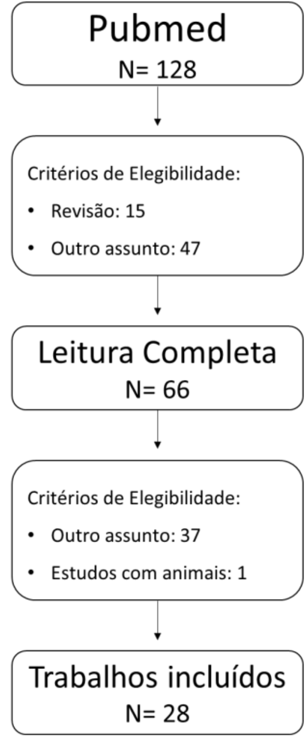
Figura 2: Fluxograma da estratégia de busca dos artigos para a revisão integrativa.



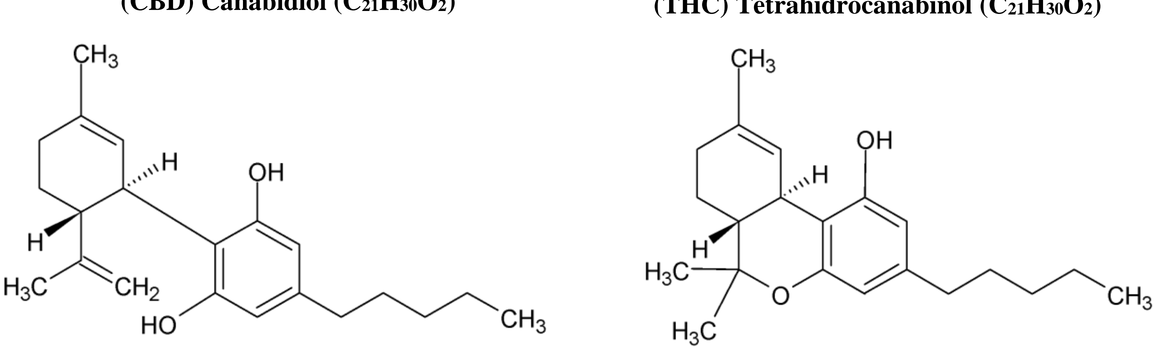
Fonte: Dados da pesquisa (2022).

3. Aspectos Farmacológicos

A Cânabis, ou Cannabis, popularmente conhecida como maconha, é uma espécie de planta do gênero Cannabis, que produz mais de 568 compostos únicos, dos quais mais de 100 pertencem à classe dos fitocanabinóides (Figura 2). Estes são moléculas orgânicas com estrutura polifenólica, que exibem uma ampla gama de ações farmacodinâmicas nos receptores canabinoides humanos (Elsohly et al., 2017; Yang et al., 2020).

Figura 3: Estruturas químicas dos principais fitocanabinóides presentes na *C.sativa*.

(CBD) Canabidiol ($C_{21}H_{30}O_2$) **(THC) Tetrahidrocanabinol ($C_{21}H_{30}O_2$)**



Fonte: Elaborada pelos autores (Software ACD/ChemSketch) (2022).

3.1 Mecanismos moleculares de sinalização via receptor canabinoide tipo 1 e tipo 2

O primeiro receptor canabinoide humano foi identificado em 1990 (Matsuda et al., 1990), sendo então parte de um sistema chamado hoje de sistema endocanabinóide (SECB), descrito como neuromodulador e importante para a manutenção da homeostase (Klumpers & Thacker, 2019).

O SECB é compreendido por vários elementos moleculares, como ligantes endógenos denominados de endocanabinóides, receptores, enzimas responsáveis pela hidrólise dos ligantes, e transportadores passivos (Rodríguez et al., 2017), conforme ilustrado na Figura 3.

Figura 4: Estruturas químicas dos endocanabinóides.

Anandamida ($C_{22}H_{37}NO_2$) **2-Araquinodilglicerol ($C_{23}H_{38}O_4$)**

Fonte: Elaborada pelos autores (Software ACD/ChemSketch) (2022).

Até o momento são reconhecidos os receptores canabinóides tipo 01 (CB1) e 2 (CB2), que são do tipo metabotrópico ligados à proteína G (Rodríguez et al., 2017). O CB1 é proeminentemente expresso nos terminais neuronais pré-sinápticos, limitados principalmente ao sistema nervoso central (SNC), e atua na modulação do processamento executivo, emocional, de recompensa e de memória, e sobre os sistemas gabaérgico, dopaminérgico e glutamatérgico. Já os receptores CB2 estão em grande parte confinados ao sistema nervoso periférico e ao sistema imunológico, onde podem influenciar na dor, inflamação e dano tecidual (Wu, 2019; Amin, 2019; Klumpers & Thacker, 2019).

Dentre os endocanabinoides mais conhecidos estão a anandamida (ANA) e 2-araquinodilglicerol (2-AG). Estes sofrem hidrólise através de enzimas conhecidas como amida hidrolase de ácido graxo (FAAH) e monoacilglicerol lipase (MAGL). Um elemento molecular adicional pertencente ao sistema endocanabinóide é o transportador de membrana de anandamida (AMT), que facilita o movimento da anandamida através da membrana celular (Rodríguez et al., 2017).

Segundo Zou e Kumar (2018), os endocanabinóides ANA e 2-AG são produzidos no terminal pós-sináptico sob demanda em resposta ao aumento da concentração intracelular de cálcio. A ANA é catalisada a partir de N-acil-fosfatidiletanolamina (NAPE) através da fosfolipase D específica de NAPE (NAPE-PLD). Já o 2-AG é produzido a partir do diacilglicerol (DAG) pela DAG lipase (DAGL) α ou β, sendo considerado o ligante primário por estar em maior quantidade no cérebro comparado a ANA (Zou & Kumar, 2018).

O SECB é um exemplo de sistema retrógrado. Os endocanabinóides são produzidos no terminal pós-sináptico, atravessam prontamente a membrana e viajam de forma retrógrada para ativar os CB1s localizados nos terminais pré-sinápticos. Os CB1s ativados inibem a liberação de neurotransmissores (NT) como GABA e glutamato, por meio da supressão do influxo de cálcio. Já a ANA tem importante função regulatória ao inibir os canais de Ca^{2+} (cálcio) do tipo L, inibir a produção de 2-AG, e ligar-se nos mesmos receptores CBs como o 2-AG (Zou & Kumar, 2018) (Figura 4).

Figura 5: Processo de sinalização canabinoide.

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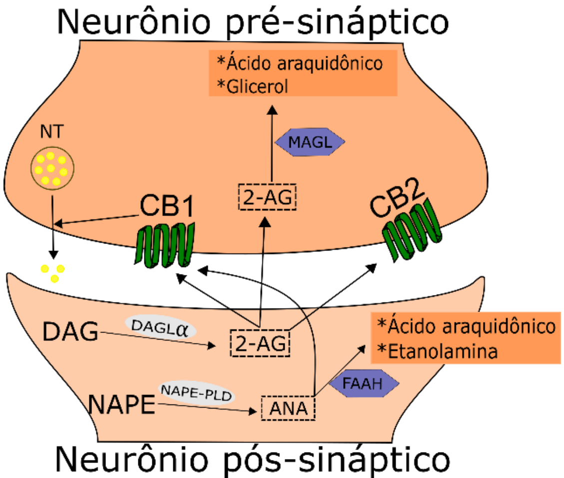

Legenda: Os endocanabinóides 2-AG e ANA são produzidos respectivamente pela DAG e NAPE no neurônio pós-sináptico. São produzidos sob demanda, em seguida são liberados na fenda e de forma anterógrada se ligam nos receptores CB1 e CB2 no neurônio pré-sináptico ligados à proteína G. Esta ligação controla o influxo de cálcio permitindo o controle da liberação de neurotransmissores (NT) na fenda sináptica, como o glutamato e dopamina. A enzima MAGL hidrolisa a 2-AG e a FAAH hidrolisa a ANA finalizando o processo de sinalização. Fonte: Adaptado de Zou & Kumar, (2018); Rodríguez et al., 2017 (Software Inkscape).

O 2-AG extra na fenda sináptica é absorvido pelos terminais pré-sinápticos e hidrolisado pela monoacilglicerol lipase (MAGL) em ácido araquidônico e glicerol, como também pode ser oxigenado pela ciclooxigenase-2 (COX-2) em ésteres glicerílicos de prostaglandina que regulam a inflamação (Sharkey & Wiley, 2016). Por outro lado, o ANA é degradado pela amida hidrolase de ácido graxo (FAAH) em ácido araquidônico livre e etanolamina (Joshi, 2019). Já a inibição de FAAH ou MAGL promove um acúmulo endógeno de ANA ou 2-AG, respectivamente, aumentando a neuromodulação (Marzo, 2018).

3.2 Localização e efeitos no trato gastrointestinal

O Trato gastrointestinal (TGI) é dotado de receptores canabinóides (CB) e de seus ligantes endógenos que são produzidos localmente de acordo com suas necessidades fisiológicas para reagir rapidamente a distúrbios no intestino e manter a homeostase (Hasenoehrl et al., 2016). Os CB1 estão localizados principalmente nos neurônios mioentéricos e submucosos, além de células epiteliais de cripta e células musculares lisas. Já os CB2 estão localizados principalmente em células epiteliais e inflamatórias, como também presentes em neurônios mioentéricos e submucosos (Camilleri, 2018).

Por meio de vias neuronais e não neuronais, o CB1 modula a motilidade do TGI, a secreção de ácidos gástricos, fluidos, neurotransmissores e hormônios, bem como a permeabilidade do epitélio intestinal (Zou & Kumar, 2018). O mecanismo de ação dos canabinóides na motilidade intestinal se dá principalmente pela ativação dos receptores CB1 expressos nos neurônios entéricos colinérgicos, deprimindo a liberação de acetilcolina, e consequentemente, causando uma diminuição da contratilidade do músculo liso intestinal (Hasenoehrl et al., 2016).

O Rimonabanto é um potente antagonista competitivo dos receptores canabinóides CB1 no intestino, responsável por aumentar o trânsito gastrointestinal. O contrário é alcançado com o Dronabinol (THC sintético), que causa atrasos no trânsito colônico (Goyal et al., 2017; Camilleri, 2018).

A inibição aguda de enzimas de síntese (DAGL∝ e NAPE-PLD) ou degradação (FAAH ou MAGL) de endocanabinóides também modula a motilidade intestinal (Hasenoehrl et al., 2016). Dismotilidades gastrointestinais foram associadas à expressão ou atividade exacerbada de CB1 e CB2, e a diminuição da atividade entérica de FAAH foi associada à constipação (Maselli & Camilleri, 2021).

Na inflamação intestinal há aumento da expressão dos receptores CB1, CB2, e da Anandamida, enquanto os níveis de FAAH são reduzidos na fase inicial da colite. Assim, o agonista do receptor CB2 foi mais eficaz em melhorar os limiares de dor de maneira dependente da dose. As preparações de cânabis desempenham um papel anti-inflamatório na doença de Crohn e colite ulcerativa e tem sido usada para tratar anorexia, dor abdominal, vômitos, gastroenterite, diarreia e gastroparesia

diabética, porém limitada devido aos efeitos psicotrópicos. Já o Canabidiol e Canabigerol compartilham os efeitos benéficos típicos dos canabinóides no intestino sem exercerem quaisquer efeitos psicotrópicos (Goyal et al., 2017; Hasenoehrl et al., 2016).

4. Estudos Clínicos

A maioria dos estudos teve como objetivo verificar características farmacocinéticas do Tetra-hidrocanabinol (THC) nos diferentes fluidos corporais, comparando a biodisponibilidade determinada por diferentes vias de administração (Newmeyer et al., 2017; Vandrey et al., 2017). O perfil farmacocinético da cânabis é essencial para compreender e interpretar os testes de toxicologia para detecção de uso recente, testes de drogas e ensaios clínicos de tratamentos (Vandrey et al., 2017).

Outro ponto de destaque nesses estudos, é a busca por formas alternativas de detecção, comparando os níveis no sangue e saliva. Para isso, foram demonstradas diversas maneiras de aferir as concentrações, sendo a maioria na saliva e no sangue. Os trabalhos procuraram estabelecer uma maneira mais fidedigna de aferição pois a forma do consumo difere muito em relação à concentração e os efeitos subjetivos da droga. Os resultados destacam um atraso na biodisponibilidade de THC na corrente sanguínea quando ocorre ingestão por via oral (Newmeyer et al., 2017; Vandrey et al., 2017). Esse atraso na biodisponibilidade pode refletir em casos de intoxicação (Loflin et al., 2017).

Em nenhum deles foi apontada a melhor forma de aferição, sejam para fins policiais, trabalhistas, de competição ou análise terapêutica, mas, foram demonstrados que diversos aspectos, como a forma ingerida (oral ou fumada), o sexo, o tempo de uso, e entre outros aspectos interferem na concentração sérica final de THC (Spindle et al., 2020). Os trabalhos analisados apresentaram várias limitações, entre elas, número de participantes e restrições judiciais quanto ao uso da substância, que restringem muitos estudos.

Na Tabela 1 é apresentada informações sobre estudos clínicos utilizando comestíveis à base de Cânabis encontrados na literatura, levando em consideração os critérios de inclusão e exclusão da pesquisa.

Tabela 1: Estudos clínicos utilizando comestíveis à base de Cânabis.

Título	Autoria	Principais objetivos	Materiais e métodos	Resultados/Discussão
Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Δ9-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration	Newmeyer et al., 2017	Predizer a concentração de 9-Tetra-hidrocanabinol no sangue e fluido oral após o consumo de Brownie de Cânabis, através de métodos de triagem. Estabelecer um método padrão de identificação da concentração de canabinóides, pela concentração sanguínea ou saliva	Adultos de 18 - 50 anos com autorrelato de uso de Cânabis, onde foi administrado uma dose inteira de cânabis oral em preparo de Brownie e ficando em unidade de pesquisa por 48 horas, sendo coletadas amostras de sangue e da saliva em preparos específicos	Todos os participantes da pesquisa testaram positivo para THC por até 5 horas após a dose oral administrada É possível identificar derivados canabinoides em um nível de concentração máxima de 0,8 a 8 horas após a vaporização, enquanto que por via oral é possível detectar entre 1 e 5 horas mais tarde.
Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration	Newmeyer et al., 2017	Comparar a quantidade de monóxido de carbono expirada, no ato de fumar, comer ou vaporizar produtos de cânabis. Aferir e comparar medidas fisiológicas	Adultos de 18 a 50 anos foram submetidos ao ensaio com a administração de cânabis na forma oral, fumada ou vaporizada, ou administração de placebo, e verificados os objetivos.	Maior concentração do sangue na cânabis fumada em comparação com a oral, devido à degradação do THC no ácido gástrico. O nível sérico de 11-OH-THC é maior quando consumido de forma oral em comparação a forma isolada
Evaluation of divided attention psychophysical task performance and effects on pupil sizes following smoked, vaporized and oral cannabis administration	Newmeyer et al., 2017	Comparar aspectos psicofísicos da atenção dividida, do desempenho em tarefas e tamanho das pupilas, na maconha fumada, oral e vaporizada.	Os participantes consumiram cânabis oral, fumada ou vaporizada por 10 minutos, sendo coletada uma amostra de sangue antes e uma outra amostra 72h após o consumo.	Em todas as formas de consumo foram identificados problemas de condução e direção. No consumo oral foi observado um maior risco de psicose, sem mecanismo conhecido. Não foram observadas alterações muito significativas no teste de Romberg (equilíbrio). Em todas as formas houve alteração do andar e caminhar, sendo mais acentuado nos usuários ocasionais e mais relacionado ao consumo oral. O tamanho médio das pupilas após 1,5 e 3,5h foi de 3,3mm e 3,4mm após o placebo, comparado a 3,6mm e 3,8mm com o uso de cânabis oral.
Placebo Effects of Edible Cannabis: Reported Intoxication Effects at a 30-Minute Delay	Loflin et al., 2017	Relatar os efeitos do cânabis comestível Determinar a intoxicação por formas comestíveis de cânabis	Os participantes receberam de forma aleatória um pirulito placebo, um com altas doses e outro com baixas doses de tetrahidrocanabinol (THC) e após isso foram coletados os auto relatos e aferidas as alterações.	Foi notado efeito placebo em pessoas que não receberam cânabis quando informado que havia THC na amostra. O principal efeito foi a diminuição do humor negativo retornando a linha de base 60 minutos após. Foi notado início de ação dos efeitos 30 min após a ingestão em alguns participantes, e, em outros, de 90 a 120 min após a ingestão.
Pharmacokinetic Profile of Oral Cannabis	Vandrey et al., 2017	Caracterizar a farmacocinética de Cânabis após a administração oral.	Participantes entre 18 e 45 anos com histórico de uso de cânabis, mas sem	O estudo conclui que há uma diferença drástica na concentração de THC na saliva, quando comparamos a via de administração de

in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes			utilizar ela e outras substâncias ilícitas nos 3 meses anteriores ao estudo. Um total de 18 participantes, entre eles 9 homens e 9 mulheres. Foram ofertadas 3 doses diferentes de THC, 10, 24 e 50 mg. Foram coletadas amostras de sangue, urina, saliva ao longo de 9 dias, e uma amostra de cabelo no 1º e 9º dia, sendo realizados os testes farmacocinéticos.	Cânabis, se comestível ou fumada, sendo a primeira forma de apresentação a que apresentou as maiores concentrações da substância na saliva. Os participantes relatam efeitos subjetivos da droga apenas com a ingestão de mais de 25mg, mesmo o estudo mostrando concentrações séricas suficientes para provar efeito nas 3 doses administradas. O tempo médio de duração dos efeitos da droga foram maiores na forma oral em comparação à fumada.
Pharmacokinetics of Cannabis Brownies: A Controlled Examination of Δ9-Tetrahydrocannabinol and Metabolites in Blood and Oral Fluid of Healthy Adult Males and Females	Spindle et al., 2020	Relatar a farmacocinética de THC em adultos através de um estudo controlado usando cânabis comestível. Verificar a variabilidade interindividual na absorção e eliminação de THC.	Os participantes ingeriram 4 doses separadas de Cânabis (0, 10, 25 e 50 mg THC) com uma semana de intervalo entre elas. Além disso, os participantes se abstiveram do uso de Cânabis por 2 meses antes do estudo. Foram coletadas amostras de sangue e saliva para estudo da farmacocinética do THC.	A concentração máxima de THC sanguíneo demorou mais para ser alcançada quando cânabis era consumida de forma oral quando comparado ao fumado. A concentração de THC na saliva foi muito maior que a concentração sanguínea. Mulheres apresentaram maiores concentrações de canabinóides no sangue em comparação aos homens, quando administrada a mesma dose na forma oral.

Fonte: Autores (2022).

5. Efeitos Gerais e Intoxicação

Os efeitos gerais da cânabis comestível podem ser divididos em efeitos subjetivos positivos, como sentimentos agradáveis, felicidade, relaxamento, energia, aumento do desejo sexual, criatividade, social, e efeitos negativos, como dificuldade de concentração, ansiedade, sonolência, vertigem, perda de controle, preguiça e sintomas gastrointestinais. Além disso, há o fator de gravidade que pode trazer riscos à saúde, como condução prejudicada e transtornos psiquiátricos (Boisvert et al., 2020).

O tetrahidrocanabinol em altas doses pode causar psicose dose-dependente aguda e transitória com sintomas positivos e negativos da esquizofrenia, como também pode aumentar o risco de desenvolver esquizofrenia propriamente dita em até duas vezes (Volkowet al., 2016). Embora os efeitos negativos da cânabis sejam bem conhecidos para algumas condições, como a exacerbação da psicose associada ao THC, outros provavelmente surgirão à medida que mais pacientes forem expostos à cânabis, como interações medicamentosas negativas, ao exemplo do aumento mediado pelo THC no tempo de sangramento em pacientes em uso de varfarina (Volkow & Ruben, 2019).

As preparações comestíveis de cânabis podem resultar em riscos maiores que as preparações inaláveis devido à lenta taxa de absorção do THC ingerido por via oral. O pico do nível sanguíneo do THC inalado e os efeitos da droga são alcançados em cerca de 30 minutos, diferindo dos comestíveis, que são alcançados em aproximadamente 3 horas. Isto torna mais difícil para os usuários de cânabis comestível titular as doses necessárias para atingir os efeitos desejados da droga, além do que a depuração mais lenta do THC oral pode levar ao acúmulo da droga se os usuários tomarem doses adicionais quando não sentirem os efeitos desejados tão rapidamente quanto esperado (Volkow & Ruben, 2019).

6. Perspectivas Terapêutica de Comestíveis à Base de Canabis

Para averiguar os novos estudos que buscam avaliar clinicamente os efeitos do consumo de comestíveis a base de Cânabis foi realizado um levantamento no site *Clinical Trials* do governo americano. Foram encontrados quatro ensaios clínicos que estão ainda no processo de recrutamento de voluntários para o estudo. Interessantemente, estes estudos buscam avaliar os possíveis efeitos terapêuticos de comestíveis à base de Cânabis em diversos processos patológicos, como câncer, ansiedade, inflamação e dor crônica.

O primeiro estudo identificado como “NCT03491384”, busca compreender os efeitos ansiolíticos, cognitivos, e propriedades anti-inflamatórias da cânabis em pacientes com ansiedade leve a moderada, após ingestão de alimentos à base de maconha e flor defumada. O segundo estudo “NCT03522103”, busca examinar a influência da cânabis no estado mental e físico dos pacientes com base na proporção de THC ou CBD, diferenciando o consumo por via oral ou inalatória. O estudo “NCT03617692” é observacional entre pacientes com câncer que já consomem alimentos à base de Cânabis como forma de tratamento dos sintomas da doença, e verifica os efeitos agudos do produto no quadro. Por fim, o estudo “NCT03522324” observa os efeitos de comestíveis a base de Cânabis no alívio da dor, inflamação e disfunção cognitiva, nos diferentes níveis de THC e CBD no sangue em pacientes com dor crônica.

Nenhum destes estudos possui resultados divulgados ainda, porém espera-se que a contribuição deles traga esclarecimentos sobre o uso de comestíveis a base de Cânabis como recursos terapêuticos no tratamento das mais diversas patologias.

7. Considerações Finais

De acordo com a pesquisa realizada, é necessário que sejam realizados um número maior de ensaios clínicos com canabis por via oral, nas diversas formulações existentes, para melhor compreender sua farmacocinética e potencialidades.

Atualmente, alguns estudos clínicos buscam investigar o potencial terapêutico de produtos alimentícios com extratos de canabis. Outro ponto, é a urgência de padronização nos comestíveis de canabis, somente assim será possível explorar todo seu potencial terapêutico.

Os ensaios clínicos com produtos alimentícios à base de extratos de Cannabis são promissores, porém carecem ainda de padronização. Cada produto é feito, na maioria das vezes, de forma artesanal, com extratos de Cannabis preparados de forma e com condições diferentes. Mesmo a forma de quantificar metabólitos difere. É preciso trabalhar com extratos padronizados que permitam a comparação de diversos estudos. Nesse sentido, a criação de extratos padronizados possibilitará avanços significativos na pesquisa com produtos alimentícios à base de Cannabis, possibilitando a expansão do mercado, e desenvolvimento de produtos alimentícios terapêuticos à base de Cannabis.

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ABSTRACT

Stevia urticifolia Thunb. is an underexploited herb possessing bioactive flavonoids, saponins, and terpenoids. The aim of this study was to examine the antiproliferative

parts (EtAcSur) upon *Artemia salina*, erythrocytes, *Allium cepa* and sarcoma 180 cells and fibroblasts, as well as *in vivo* studies on mice to determine systemic, macroscopic, and behavioral alterations and bone marrow chromosomal damage. The assessment using *A. salina* larvae and mouse blood cells revealed LC_{50} and EC_{50} values of 68.9 and 113.6 µg/ml, respectively. Root growth and mitosis were inhibited by EtAcSur, and chromosomal aberrations were detected only at 100 µg/ml. EtAcSur exhibited potent concentration-dependent viability reduction of S180 and L-929 cells and antioxidant capacity employing $ABTS^{\bullet}$ and $DPPH^{\bullet}$. No previous *in vivo* studies were performed before with the EtAcSur. Signals of acute toxicity were not observed at 300 mg/kg. Physiological and toxicological investigations at 25 and 50 mg/mg/day i.p. for 8 days did not markedly change body or organ relative weights, nor patterns of spontaneous locomotor and exploratory activities. In contrast, clastogenic effects on bone marrow were found at 50 mg/mg/day. EtAcSur was found to (1) produce toxicity in microcrustaceans, (2) capacity as free radical scavenger, (3) antimitotic, cytotoxic and clastogenic activties upon vegetal and mammalian cells, and (4) lethality on both tumor and normal murine cells indistinctly. *In vivo* damage systemic effects were not remarkable and clinical signals of toxicity were not observed, suggesting the significant pharmacological potential of *S. urticifolia* for the development of antineoplastic agents.

Abbreviations: ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DMSO: dimethylsulfoxide; DPPH: 1,1-diphenyl-2-picrylhydrazyl; EC_{50}: effective concentration 50%; EtAcSur: ethyl acetate extract from *Stevia urticifolia* aerial parts; Hb, hemoglobin; IC_{50}: inhibitory concentration 50%; LC_{50},: lethal concentration 50%; MI: mitotic index; RBC, red blood cells; Trolox: 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

KEYWORDS: *Allium cepa* chemoprevention *in vivo* toxicity genotoxicity sarcoma 180

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Data availability statement

Raw data were generated at GraphPad Prisma. Derived data supporting the findings of this study are available from the corresponding author [P.M.P.F.] on request.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethics approval

The registry in SisGen (*Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado* – National System of Management of Genetic Heritage and Associated Traditional Knowledge: #AF467FD) according to the Brazilian Federal Law No 13,123/2015 about access to the national biodiversity (Brazil 2015). All protocols involving animals were approved by the Ethical Committee on Animal Experimentation at UFPI (CEUA #008/2015 and #0555/2019) and followed Brazilian (*Sociedade Brasileira de Ciência em Animais de Laboratório* - SBCAL) and International (Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes) rules on the care and use of experimental animals.

The work described has not been previously published or submitted for publication elsewhere. The publication is approved by all authors.

Additional information

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PDFA (English)

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4507.p1-5.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4121.p1-8.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4513.p1-5.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4487.p1-6.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4200.p1-8.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4268.p1-7.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4461.p1-6.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4184.p1-5.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4196.p1-10.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.3794.p1-4.2022

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DOI: https://doi.org/10.12662/2317-3076jhbs.v10i1.4374.p1-4.2022

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PDFA (English)

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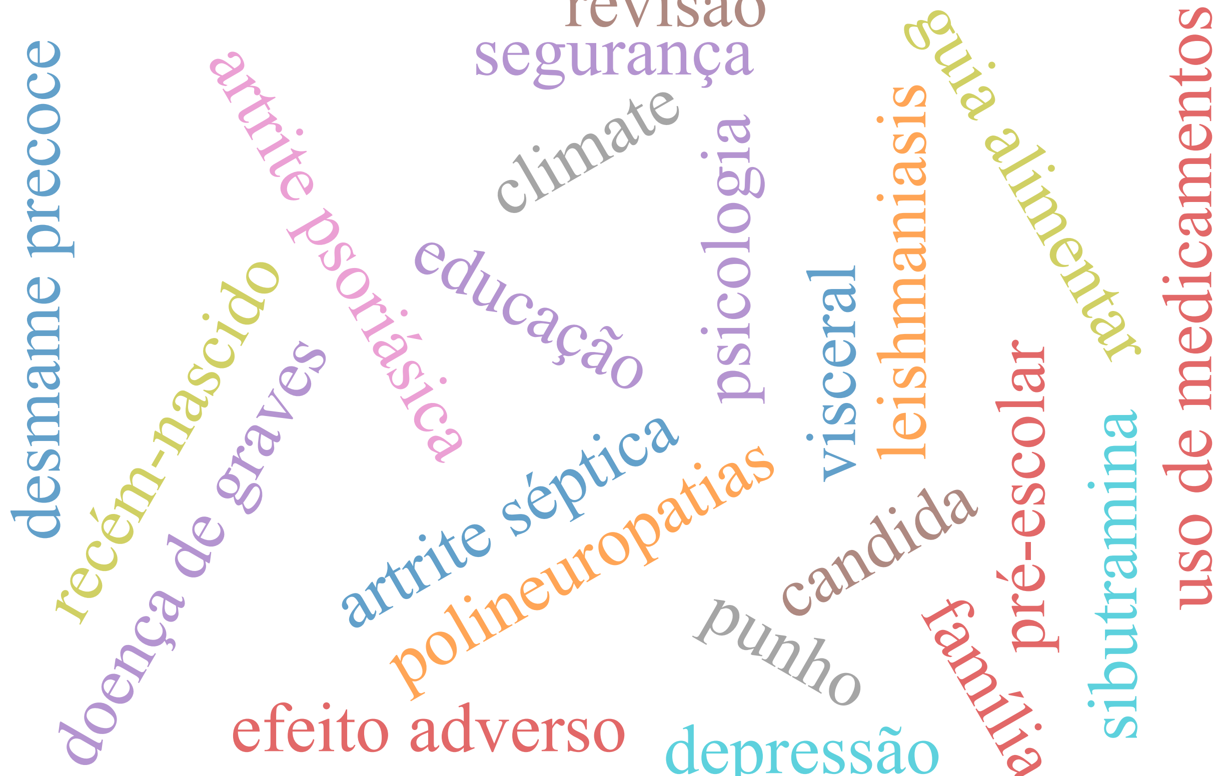
PDFA (English)

Enviar Submissão

Idioma

- English
- Español (España)
- **Português (Brasil)**

Palavras-chave



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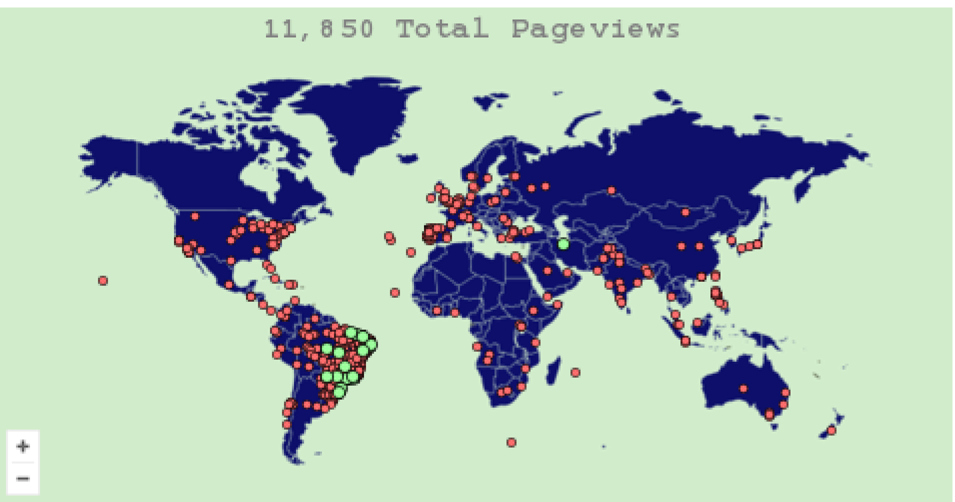

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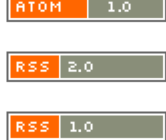

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ORIGINAL ARTICLE

Mutagenic Evaluation of Fluoxetine and Fluoxetine-Galactomannan Complex Through the Analysis of Chromosomal Aberrations in Human Peripheral Leukocytes and *Salmonella typhimurium*/Microssome Assay

Avaliação Mutagênica de Fluoxetina e Complexo Fluoxetina-Galactomanana Através da Análise de Aberrações Cromossômicas em Leucócitos Periféricos Humanos e em *Salmonella typhimurium* / Ensaio Microssômico

Bruno Coêlho Cavalcanti[1,2], Cecília Rocha da Silva[1,3], João Batista de Andrade Neto[1,3,5], Maria Aparecida Alexandre Josino[3], Lívia Gurgel do Amaral Valente Sá[1,3,5], Antônio Adailson de Sousa Silva[1], Francisco Stefânio Barreto[1], José Roberto de Oliveira Ferreira[6], Hemerson Iury Ferreira Magalhães[7], Ícaro Gusmão Pinto Vieira[4], Débora Hellen Almeida Brito[4], Nágila Maria Pontes Silva Ricardo[4], Fátima Daiana Dias Barroso[1,3,5], Érica Rayanne Mota da Costa[3,5], Hélio Vitoriano Nobre Júnior[1,3], Manoel Odorico de Moraes[1,2]

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Abstract

Objectives: The purpose of this study was to evaluate the mutagenic potential of fluoxetine and fluoxetine-galactomannan. Methods: Chromosomal aberration test and *Salmonella typhimurium*/microsome mutagenicity assay. Results: The results showed that fluoxetine (250 µg/mL) can cause chromosomal breaks of treated leukocytes and increase the frequency of reversion of the tester strains of *S. typhimurium* / microsome assay only at the highest concentration (5 mg/mL), while fluoxetine encapsulated in galactomannan did not cause these changes (leukocytes and *S. typhimuriums* strains). Conclusion: In summary, fluoxetine showed a mutagenic effect detectable only at high concentrations in both eukaryotic and prokaryotic models. Furthermore, the fluoxetine/ galactomannan complex, in this first moment, prevented the mutagenicity attributed to fluoxetine, emphasizing that the present encapsulation process can be an alternative in preventing these effects *in vitro*.

Keywords: Fluoxetine; Galactomannan; Mutagenicity; Chromosomal Aberrations; *Salmonella typhimurium* /Microsome Assay.

Resumo

Objetivos: avaliar o potencial mutagênico da fluoxetina e da fluoxetina-galactomanana. Métodos: Teste de aberração cromossômica e ensaio de mutagenicidade de *Salmonella typhimurium* /microssoma. Resultados: a fluoxetina (250 µg/mL) pode causar quebras cromossômicas de leucócitos tratados e aumentar a frequência de reversão das cepas testadoras de *S. typhimurium* /microssoma apenas na concentração mais alta (5 mg/mL), enquanto a fluoxetina encapsulada em galactomanano não causou essas alterações (leucócitos e cepas de *S. typhimurium*). Conclusão: a fluoxetina mostrou um efeito mutagênico detectável apenas em altas concentrações em modelos eucarióticos e procarióticos. Além disso, o complexo fluoxetina/galactomanan, neste primeiro momento, evitou a mutagenicidade atribuída à fluoxetina, ressaltando que o presente processo de encapsulamento pode ser uma alternativa na prevenção desses efeitos *in vitro*.

Palavras-chave: Fluoxetina; Galactomanana; Mutagenicidade; Aberrações cromossômicas; Ensaio de *Salmonella typhimurium* /microssoma.

INTRODUCTION

Nanoparticles (NPs) generally have different physical-chemical and electronic properties, including higher specific surface area and surface reactivity. This is mainly due to the small size of the microparticles obtained during the production process[1]. The properties of NPs can also be related to another enhanced reactivity capacity, and consequently greater ability to penetrate tissues and cell membranes[2].

The use of microparticles today can be a great ally to the quality of life, but it can also raise concerns of society, as inevitable perceived risks cannot be ignored[3]. Thus, for NPs to be considered safe, they need to be tested to verify their possible toxic effects.

For NPs applications to be beneficial, they need to be quickly

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internalized by cells[2,4]. However, NPs can also cause changes in the thickness of cell membranes, induce the formation of pores in the membrane and thus impair their integrity, and generate oxidative stress, resulting in nanotoxicity[5]. Therefore, during the processes of evaluation of NPs, it is necessary to observe the interaction with biomembranes (for example, with the cell membrane) to evaluate the ability to reach the target cells. Understanding the underlying mechanism of NPs-biomembrane interactions is important to improve the positive effects of NPs and thus avoid possible nanotoxicity.

According to [6] and the International Standardization Organization (expressed in ISO 10993), the *in vitro* cytotoxicity assay is the first test that should be used to assess the biocompatibility of any material for use in biomedical devices. Only after non-toxicity is proven can other tests be performed to complete the findings. Genotoxicity and mutagenicity assessment is also a useful component, where safety can be assessed when using certain substances, such as pharmaceuticals, industrial chemicals, pesticides, biocides, food additives, and cosmetic ingredients, all of which are relevant in the context of international regulations aimed at protecting human and animal health[7].

Fluoxetine (FLX) is one of the selective serotonin reuptake inhibitors and galactomannan (Galact) is a natural polymer with several characteristics that can be advantageous for possible biopharmaceutical applications, among them its high capacity for gelling and the absence of toxic effects[8]

It is important to evaluate the genotoxicity potential and mutagenicity of compounds consumed by humans, particularly drugs. The toxicity of fluoxetine to various cell types and tissues is clearly described in the literature[14–17.18] reported that cytotoxicity and genotoxicity are associated with ROS production.

The main goal of the present study was to analyze the mutagenic potentials of FLX and FLX-Galact on human leukocytes (chromosomal aberration assay) and bacteria (*Salmonella typhimurium*/microsome assay).

MATERIALS AND METHODS

Chemicals

Fluoxetine (FLX) was purchased from Sigma Chemical (St. Louis, MO). Fetal bovine serum, phytohemagglutinin, RPMI 1640 medium, trypsin-EDTA, glutamine, penicillin, and streptomycin were purchased from Gibco® (Invitrogen, USA). Cyclophosphamine was supplied by Asta Medica. The S9 fraction, prepared from the livers of Sprague–Dawley rats pretreated with the polychlorinated biphenyl mixture Aroclor 1254, was purchased from Moltox Inc. (Boone, NC, USA). Colchicine, L-histidine, biotin, aflatoxin B1,4-nitroquinoline-oxide (4-NQO), and methyl methanesulfonate (MMS), were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). All other chemicals and reagents used were of analytical grade.

Biomembranes

Encapsulation of fluoxetin

The formulation was prepared from a solution (1%) of the natural polymer galactomannan and stirred for 24 h at room temperature. Then fluoxetine and Tween 80 (0.1% per bioactive substance) were added and stirred for 4 h before spray drying in a Büchi B-290 spray dryer. The inlet and outlet temperatures were 120 and 90 °C, respectively. The feed flow was 10 mL/min and the aspirator flow was $35m^3/h$ [8] as described in [23].

The final proportion of polymer: bioactive was 90:10 w/w. The operational yield was 37%. The sample was stored with protection from humidity and light [8,9].

Isolation of peripheral blood leukocytes (PBLs)

The present study was approved by our university's research ethics committee (Process No. 161/2014). Heparinized blood was collected from healthy non-smoking donors who had not taken any medication in the 15 days before sampling and who had no history of exposure to potentially genotoxic substances. PBLs were isolated by the standard method of density-gradient centrifugation over Histopaque-1077. Cells were washed and resuspended in RPMI 1640 medium supplemented with 20% fetal bovine serum, 2 mM glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin, at 37 °C under 5% CO2. Phytohemagglutinin (2.5%) was added at the beginning of the culture. After 24 hours, cells were treated with the test substances.

Chromosomal aberrations (CAs) test

After the end of treatment (24 hours) with FLX and FLX-Galact at concentrations of 100 and 250 µg/mL, determined from tests carried out previously with microparticles of galactomannan/fluoxetine against methicillin-resistant *S. aureus*[23], cells were washed with ice-cold PBS and re-cultivated in a complete RPMI medium for 48 h. Colchicine (0.0016%) was added 2 hours before fixation (72 h). Chromosomes were prepared according to standard procedures 10. Hypotonic treatment with KCl (0.75 M, 37 °C) was applied for 15 min. The cells were fixed with methanol and acetic acid (3:1), and the fixative solution was changed twice. Air-dried slides were stained with Giemsa (5%, pH 6.8) for 7 min and scored for CAs according to[11]. MMS (4 x 10-5 M), reference substance that has mutagenic character[22], and cyclophosphamide (50 µg/mL) were used as positive controls. Only well-spread metaphases were examined. One hundred and fifty metaphases per culture were analyzed for the presence of CAs. The mitotic index was determined for 2,000 cells and expressed as the number of mitoses per 100 cells (%)[12].

S. typhimurium /microsome mutagenicity assay

S. typhimurium TA98, TA97a, TA100, and TA102 were kindly provided by B. M. Ames (University of California, Berkeley,

CA, USA). Mutagenicity was assayed by the pre-incubation procedure. The S9 metabolic activation mixture (S9 mix) was prepared according to 13. Briefly, 100 µL of test bacterial cultures (1-2 x 10 9 cells/mL) were incubated at 37°C with FLX and FLX-Galact, at concentrations of 2500 and 5000 µg/plate, dissolved in water in the presence or absence of S9 mix for 20 min, without shaking. Subsequently, 2 mL of soft agar (0.6% agar, 0.5% NaCl, 50 M histidine, 50 M biotin, pH 7.4, 42 °C) was added to the test tube and the content was poured immediately onto a plate of minimal agar (1.5% agar, Vogel-Bonner E medium, containing 2% glucose). Aflatoxin B1 (1 µg/plate) was used as a positive control for all strains (in the presence of metabolic activation with S9 mix), 4-nitroquinoline-oxide (4-NQO, 0.5 µg/plate) for TA97a, TA98, and TA102, and sodium azide (1 µg/plate) for TA100 (absence of S9 mix). Plates were incubated in the dark at 37 °C for 48 h before counting the revertant colonies.

Statistical analysis

All experiments were performed independently three times. All statistical analyses were carried out using the GraphPad program (Intuitive Software for Science, San Diego, CA). For the chromosomal aberration test, data are presented as means ± SD and were compared by analysis of variance (ANOVA) followed by Tukey's test.

Salmonella/microsome mutagenicity data were analyzed using the Salmonel software. A compound was considered positive for mutagenicity only when: (a) the number of *revertants* was at least twice the spontaneous yield (MI ≥ 2; MI = mutagenic index: number of induced colonies in the sample/number of spontaneous colonies in the negative control samples); (b) a significant response was obtained in the analysis of variance ($p \leq 0.05$); and (c) a reproducible positive dose response ($p \leq 0.01$) was present, as evaluated by the Salmonel software.

RESULTS

Encapsulation of fluoxetin

Analysis of genetic changes at the chromosomal level induced by FLX and FLX-Galact on cultured PBLs

Table 1 shows chromosomal and numerical aberrations in cultured PBLs in the presence or absence of the S9 fraction of FLX and FLX-Galact. A slight increase in chromosome and chromatid ruptures were observed only in cultures treated with 250 µg/mL FLX in the absence of S9 mix. Moreover, numeric chromosomal changes like polyploidy and endoreduplication were not observed in any experimental cultures (FLX and FLX-Galact). Regarding cytotoxicity, FLX only at a concentration of 250 µg/mL caused a slight reduction ($p < 0.05$) in the mitotic index (cell proliferation), which was indicative of weak toxicity. This was not observed in FLX-Galact at both concentrations (100 and 250 µg/mL) in the presence or absence of the S9 fraction.

Table 1. Mitotic index, frequency of chromosomal aberrations, and numeric changes in cultured human PBLs after FLX and FLX-Galat exposure with and without metabolic activation (S9 fraction).

Compounds	S9 mix	Treatments	Mitotic index (%)[c]	Number of aberrations[d]			Aberant cells (%) [e]
				R	P	E	
Vehicle[a]	-	0.1%	6,39 ± 0,55	0	0	0	0
MMS[b]	-	4 x 10-5 M	2,84 ± 0,20*	29	0	0	9,66 ± 0,81*
Cyclophosphamide[b]	-	50 µg/mL	5,91 ± 0,55	3	0	0	1,33 ± 0,15
FLX	-	100 µg/mL	5,73 ± 0,21	1	0	0	0,44 ± 0,11
	-	250 µg/mL	5,22 ± 0,15*	5	0	0	2,21 ± 0,27*
FLX-Galat	-	100 µg/mL	6,27 ± 0,20	0	0	0	0
	-	250 µg/mL	5,95 ± 0,10	3	0	0	1,33 ± 0,15
Vehicle[a]	+	0.1%	6,83 ± 0,27	1	0	0	0,44 ± 0,11
MMS[b]	+	4 x 10^{-5} M	2,77 ± 0,56*	22	0	0	7,32 ± 0,56*
Cyclophosphamide[b]	+	50 µg/mL	3,96 ± 0,22*	18	0	0	5,99 ± 1,15*,#
FLX	+	100 µg/mL	5,78 ± 0,17	0	0	0	0
	+	250 µg/mL	5,62 ± 0,20	3	0	0	1,33 ± 0,15
FLX-Galat	+	100 µg/mL	6,41 ± 0,10	1	0	0	0,44 ± 0,11
	+	250 µg/mL	6,17 ± 0,25	0	0	0	0

[a]DMSO; [b]Positive controls; [c]determined for 2,000 cells (means ± SD); [d]number of aberrations per 150 metaphases analysed: R, ruptures (chromosome and chromatid); P, polyploid cells; E, endoreduplication); [e]percentage of cells with at least one aberration; *$p < 0.05$ compared to vehicle group by ANOVA followed by Tukey test. Data are presented as means ± SD for three independent experiments in triplicate; #$p < 0.05$ compared to experiments conducted in the absence of S9 mix by ANOVA followed by Tukey test. Data are presented as means ± SD for three independent experiments in triplicate.

Reversion analysis of mutations induced by FLX and FLX-Galact assessed by Salmonella/microsome mutagenicity assay

FLX and FLX-Galact were first tested for TA100 strain toxicity at concentrations of 1000-5000 µg/plate in the Salmonella/microsome assay. The range-finding results indicated no cytotoxicity at concentrations up to 5000 µg\mL in FLX. However, in the Salmonella/microsome assay, only FLX at 5000 µg\mL induced a significant increase (p<0.05) in the rate of reversion in all strains tested in the presence or not of exogenous metabolic activation (Tables 2 and 3). No mutagenic effect was observed for bacterial cultures treated with FLX-Galact at concentrations of 2500 and 5000 µg\mL. Highlighting the absence of mutagenic effect in bacterial systems in the presence or not of the metabolizing S9 fraction (Tables 2 and 3).

Table 2. Induction of his+ revertants in TA98 and 97a S.typhimurium frameshift strains by FLX and FLX-Galat with and without metabolic activation (S9 fraction).

		S. typhimurium							
		TA98				TA97a			
		-S9		+S9		-S9		+S9	
Compounds	Treatments	Rev/plate[c]	MI[d]	Rev/plate[c]	MI[d]	Rev/plate[c]	MI[d]	Rev/plate[c]	MI[d]
Vehicle[a]	0.1%	27,81 ± 8	-	31,15 ± 2	-	245,02 ± 48	-	208,37 ± 20	-
PC[b]		293,50 ± 75*	10,85	512,68 ± 154*	16,51	836,57 ± 139*	3,46	689,28 ± 118*	3,31
FLX	2500 µg/plate	12,64 ± 3	0,44	21,75 ± 7	0,67	230,28 ± 77	0,93	263,10 ± 51	1,26
	5000 µg/ plate	59,47 ± 11*	2,18	85,24 ± 15*	2,74	499,46 ± 111*	2,05	427,55 ± 95*	2,05
FLX-Galat	2500 µg/ plate	17,38 ± 5	0,62	32,91 ± 2	1,03	234,72 ± 37	0,95	266,24 ± 73	1,27
	5000 µg/ plate	35,02 ± 5	1,29	49.0 3 ± 9	1,58	252,15 ±5 5	1,02	294,16 ± 88	

aWater;
bPositive control: (-S9) 4-nitroquinoline 1-oxide (0.5 µg/plate); (+S9) aflatoxin B1 (1 µg/plate)
cNumber of revertants/plate presented as means ± SD for three independent experiments in triplicate
dMI: mutagenic index (number of his+ induced colonies in the sample/number of spontaneous his+ colonies in the negative control)
*p < 0.05 compared to vehicle group.

Table 3. Induction of his+ revertants in TA100 and 102 S.typhimurium frameshift strains by FLX and FLX-Galat with and without metabolic activation (S9 fraction).

		S. typhimurium							
		TA100				TA102			
		-S9		+S9		-S9		+S9	
Compounds	Treatments	Rev/plate[c]	MI[d]	Rev/plate[c]	MI[d]	Rev/plate[c]	MI[d]	Rev/plate[c]	MI[d]
Vehicle[a]	0.1%	103,48 ± 17	-	118,34 ± 32	-	347,15 ± 40	-	428,95 ± 25	-
PC[b]		571,52 ± 72*	5,54	374,50 ± 47*	3,16	2922,81 ± 218*	8,42	1131,90 ± 213*	2,64
FLX	2500 µg/plate	123,43 ± 28	1,19	139,57 ± 55	1,17	354,96 ± 63	1,02	370,26 ± 24	0,86
	5000 µg/ plate	384,60 ± 51*	3,72	475,14 ± 12*	4,02	704,48 ± 47*	2,03	952,84 ± 20*	2,22
FLX-Galat	2500 µg/ plate	111,07 ± 20	1,07	124,79 ± 31	1,05	329,61 ± 58	0,94	443,29 ± 41	1,03
	5000 µg/ plate	157,39 ± 15	1,52	203,51 ± 18	1,72	387,58 ± 37	1,11	498,35 ± 18	1,16

aWater;
bPositive control: (-S9) 4-nitroquinoline 1-oxide (0.5 µg/plate); (+S9) aflatoxin B1 (1 µg/plate)
cNumber of revertants/plate presented as means ± SD for three independent experiments in triplicate
dMI: mutagenic index (number of his+ induced colonies in the sample/number of spontaneous his+ colonies in the negative control)
*p < 0.05 compared to vehicle group.

DISCUSSION

There are several techniques available to measure mutagenicity, such as the Salmonella mutagenicity assay and tests for structural chromosome aberrations, micronuclei, and sister chromatid exchanges. Chromosome aberration analysis measures the frequency of breakages or exchange of chromosomal material including breaks in the chromosome or chromatid, rearrangements, translocations, inversions, or anaphase bridges. An increase in the frequency of chromosome aberrations is indicative of clastogenicity, which increases the risk for genetic ill health and cancer[19].

Fluoxetine is now the first choice antidepressant used to treat children and adolescents as monotherapy for unipolar depression[18]. There are a growing number of people suffering from anxiety and depression, therefore increasing the need for fluoxetine. So, verifying the absence of effects such as cytotoxicity or mutagenicity is of great importance.

Our results showed that fluoxetine caused chromosomal structural changes in PBLs only at the highest concentration (250 µg/mL), and provoke an increase in the number of colony formation in the Salmonella/microsome assay. Furthermore, encapsulating fluoxetine in galactomannan did not cause these changes, indicating encapsulation with the polymer decreases the clastogenic potential of fluoxetine at the highest concentration. Galactomannan, since it is a natural polymer, has several characteristics that can be advantageous for biopharmaceutical applications, one of which is its nontoxicity[8]. The assessment of genotoxic hazards to humans currently follows a stepwise approach, beginning with a basic battery of *in vitro* tests followed in some cases by in vivo testing[7]. Our data are preliminary, but galactomannan encapsulation can be an alternative to minimize mutagenic effects.

Cytotoxc effects of high concentrations of fluoxetine (2000 µg/mL) were found in A. cepa L.[14]. Root tip cells, probably because this type of drug affects carrier cells, resulting in cell death or inhibition of cell division. It was observed that fluoxetine promoted sister chromatid exchanges (SCE) and induced dose-dependent sperm abnormalities[15]. They also found that the highest dose tested increased SCE about two-fold and the level of control of sperm abnormalities about four-fold.

It was also shown that fluoxetine at concentrations of 0.2 and 1.0 mg/mL was not genotoxic by the comet assay in cultured Chinese hamster ovary (CHO) cells 21. However, they found fluoxetine to be genotoxic at a concentration of 5.0 mg/mL. These latter results were similar to our finding that only the highest concentration of fluoxetine (5000 µg\mL) showed mutagenic potential.

In summary, fluoxetine showed a mutagenic effect detectable only at high concentrations in both eukaryotic and prokaryotic models. Furthermore, the fluoxetine/galactomannan complex, in this first moment, prevented the mutagenicity attributed to fluoxetine, emphasizing that the present encapsulation process can be an alternative in preventing these effects *in vitro*.

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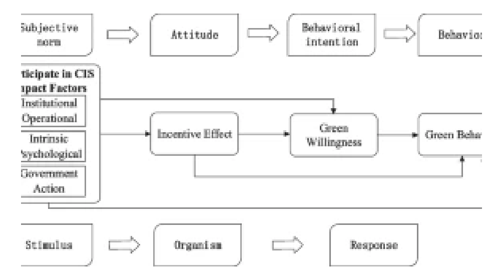

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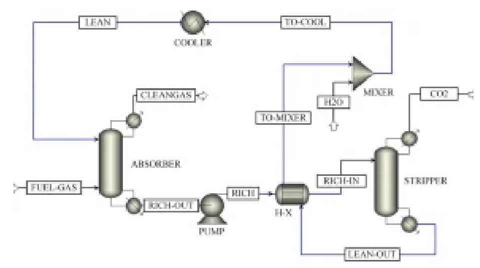

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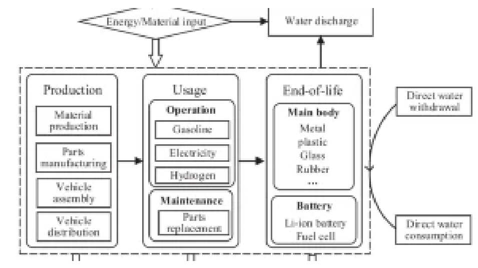

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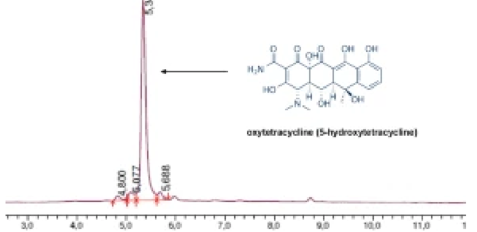

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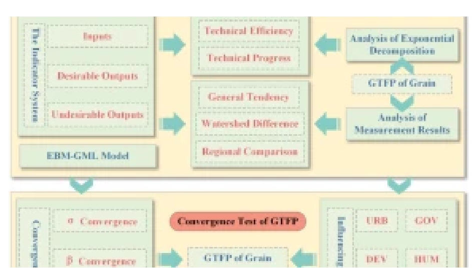

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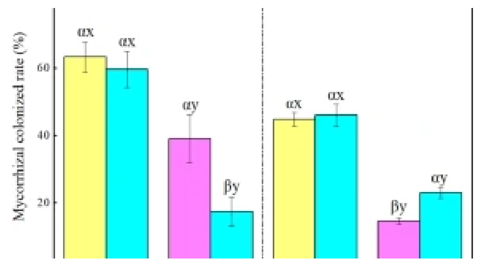

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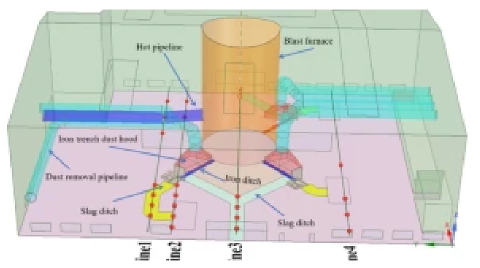

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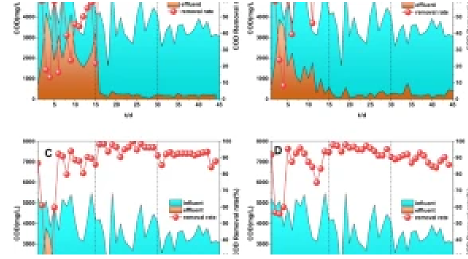

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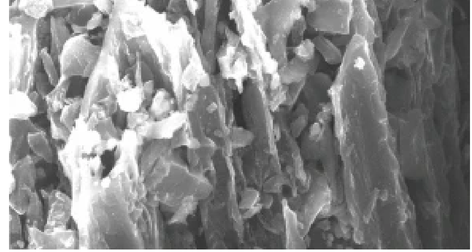

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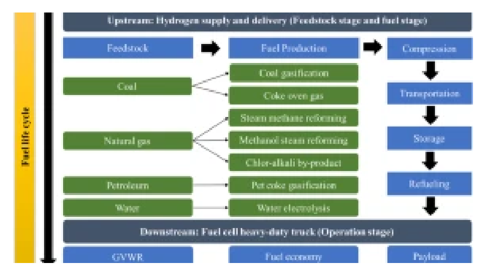

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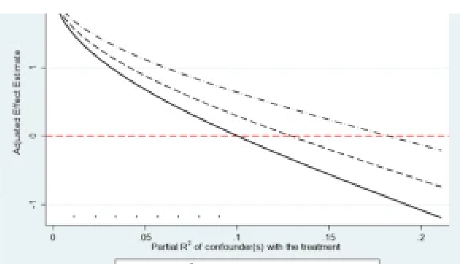

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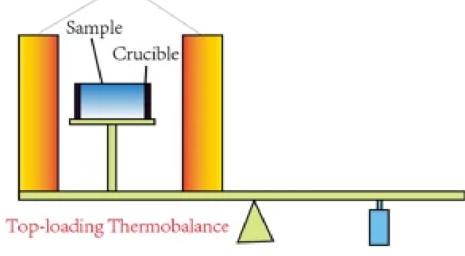

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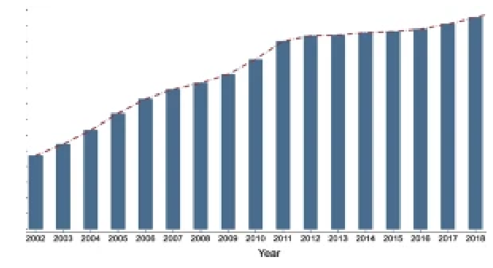

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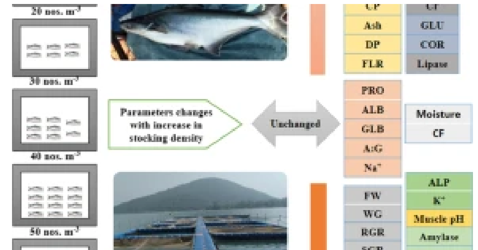

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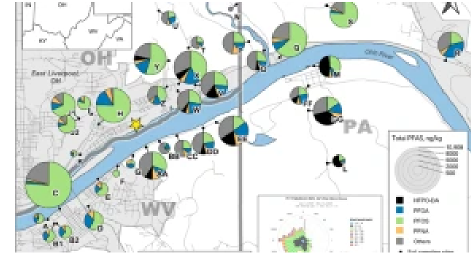

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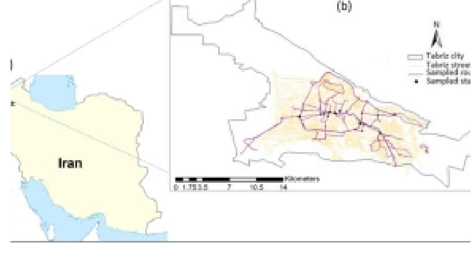

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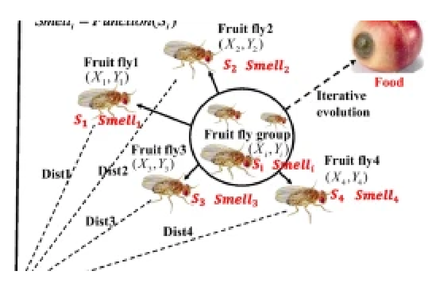

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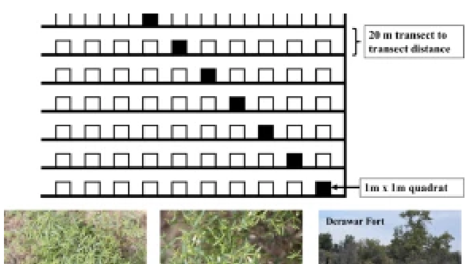

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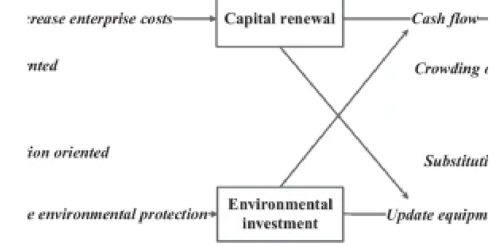

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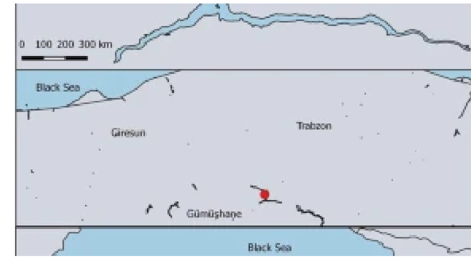

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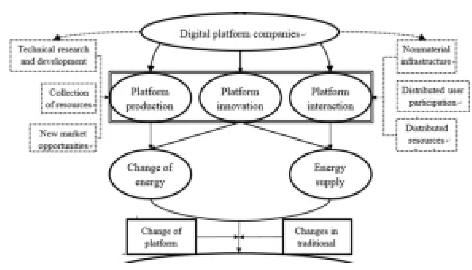

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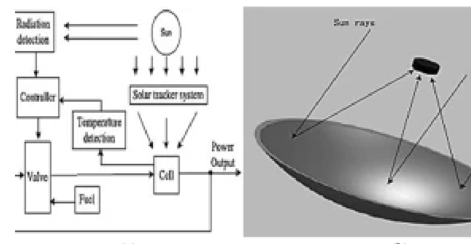

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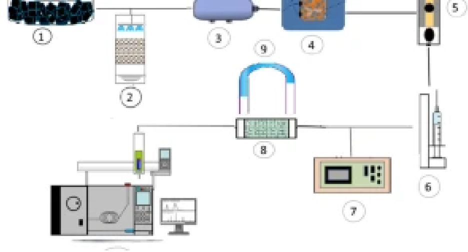

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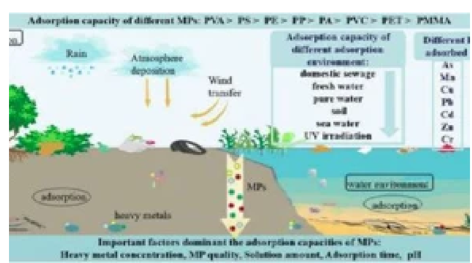

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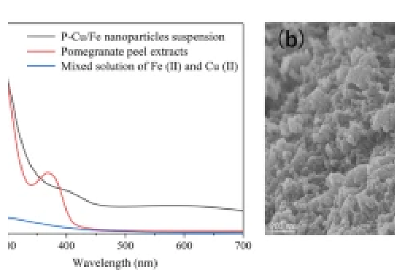

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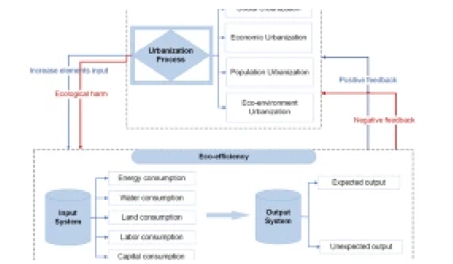

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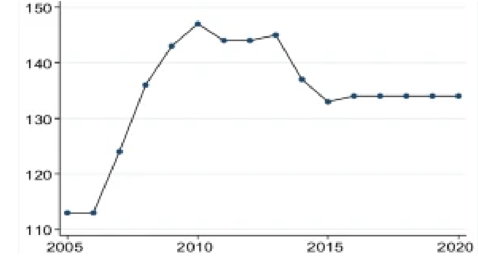

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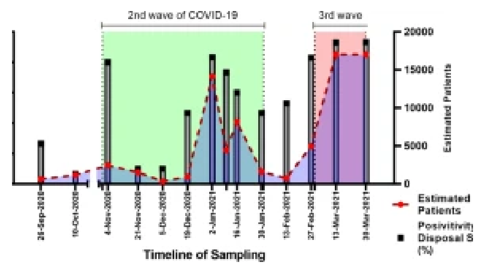

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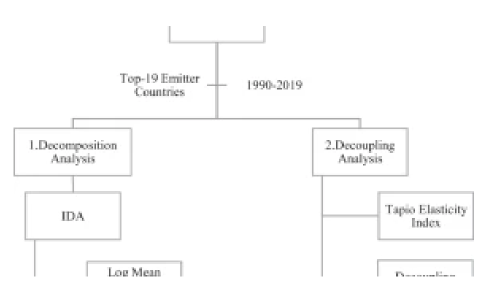

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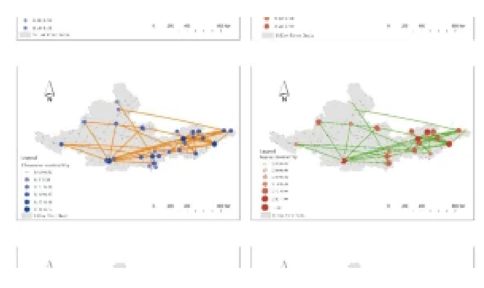

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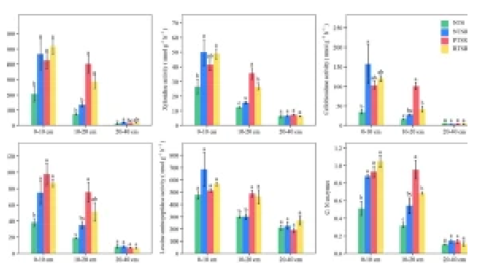

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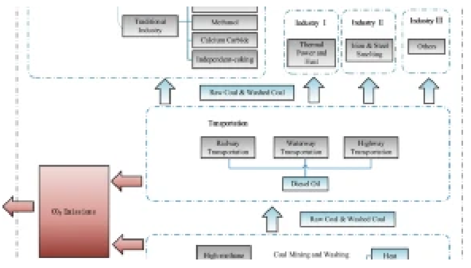

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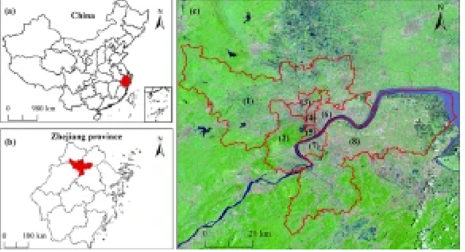

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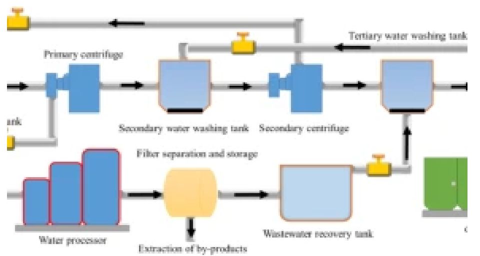

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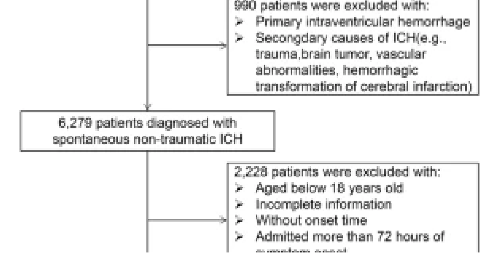

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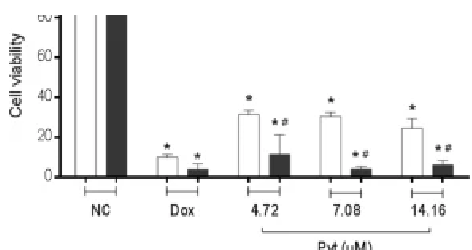

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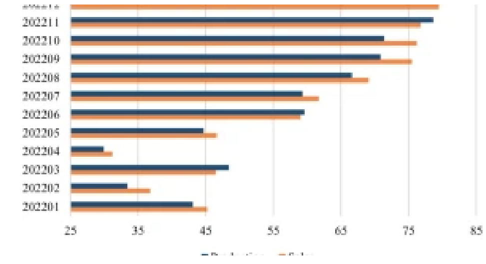

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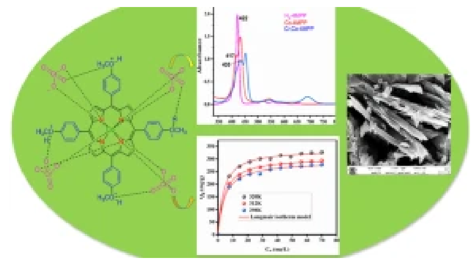

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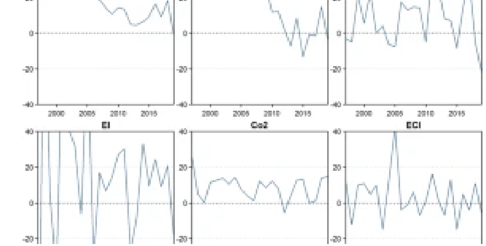

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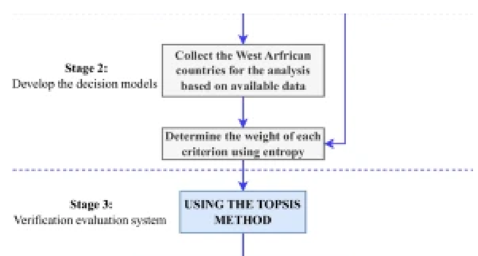

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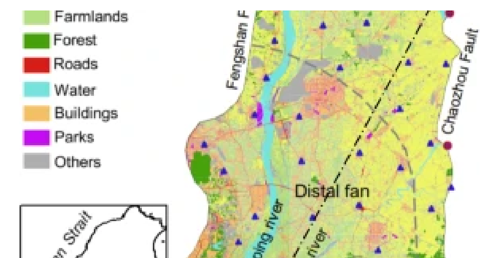

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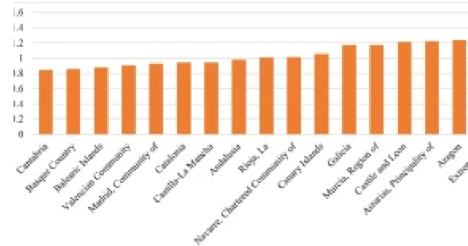

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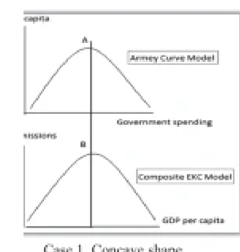
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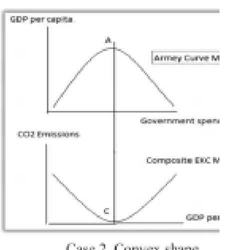
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RESEARCH ARTICLE

Anticancer effects of phytol against Sarcoma (S-180) and Human Leukemic (HL-60) cancer cells

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Abstract
Phytol (Pyt), a diterpenoid, possesses many important bioactivities. This study evaluates the anticancer effects of Pyt on sarcoma 180 (S-180) and human leukemia (HL-60) cell lines. For this purpose, cells were treated with Pyt (4.72, 7.08, or 14.16 μM) and a cell viability assay was performed. Additionally, the alkaline comet assay and micronucleus test with cytokinesis were also performed using doxorubicin (6 μM) and hydrogen peroxide (10 mM) as positive controls and stressors, respectively. Results revealed that Pyt significantly reduced the viability and rate of division in S-180 and HL-60 cells with IC_{50} values of 18.98 ± 3.79 and 1.17 ± 0.34 μM, respectively. Pyt at 14.16 μM exerted aneugenic and/or clastogenic effects in S-180 and HL-60 cells, where the number of micronuclei and other nuclear abnormalities (e.g., nucleoplasmic bridges and nuclear buds) were frequently observed. Moreover, Pyt at all concentrations induced apoptosis and showed necrosis at 14.16 μM, suggesting its anticancer effects on the tested cancer cell lines. Taken together, Pyt showed promising anticancer effects, possibly through inducing apoptosis and necrosis mechanisms, and it exerted aneugenic and/or clastogenic effects on the S-180 and HL-60 cell lines.

Keywords Phytol · Diterpenoid · Cancer cell lines · Anticancer effects

Introduction

Still, cancer remains one of the most fearful diseases worldwide, with a complex etiology that involves several biochemical, physiological, and molecular mechanisms

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(Zhang et al. 2020). Sarcomas are heterogeneous malignancies of mesenchymal origin that can occur in various tissues, such as osteosarcomas, rhabdomyosarcomas, and liposarcomas. Molecular mechanisms involved in the disease, investigated in different models, contribute to the advancement of therapies for these neoplasias (Post 2012). Generally, complex sarcomas involve multiple structural and numerical chromosomal changes, especially in epithelial sarcomas. Therefore, research is needed to elucidate cytogenetic damage (Taylor et al. 2011).

Similarly, leukemias are hematopoietic disorders that also require biological and molecular understanding, which can be studied in human cell lines such as HL-60 in the search for new natural compounds with anticancer effects (Chien et al. 2017). In this regard, it should be emphasized that there are similarities between rodents and humans regarding biological behavior and response to therapy and cytotoxic agents (Cekanova and Rathore 2014). On the other hand, drug development is still a challenge for oncology therapy due to several aspects, including the genetic heterogeneity of cancer that leads to resistance to therapies (Samadi et al. 2015).

Several studies indicate that a number of phytochemicals exhibit anti-cancer activities *via* induction of apoptosis and inhibition of cancer cell proliferation (Wu et al. 2017). To date, a number of diterpenes and their derivatives, such as manool extracted from *Salvia officinalis* (Nicolella et al. 2014), paclitaxel (Turkez et al. 2010), 7,15-trien-3-oic acid (Di Sotto et al. 2012), and taxodione (Kuźma et al. 2016), have been found to exhibit cytotoxic and genotoxic activities in different test systems. Phytol (Pyt) (3,7,11,15-tetramethyl-1-hexadecene-2-ol) is a diterpenoid with various pharmacological effects (Islam et al. 2015, 2016, 2018). Scientific reports suggest that it possesses antispasmodic (Pongprayoon et al. 1992), non-mutagenic (Kagoura et al. 1993), anti-teratogenic (Arnhold et al. 2002), antimicrobial (Inoue et al. 2005), immunoadjuvant (Lim et al. 2006), antiepileptic (Costa et al. 2012), antiprotozoal (Bero et al. 2013), anti-inflammatory (Silva et al. 2014), antioxidant (Islam et al. 2016), antidiabetic (Elmazar et al. 2013), hypolipidemic, antinociceptive (Santos et al. 2013), antipyretic (Islam 2019), anti-depressive (Costa et al. 2011), as well as cytogenotoxic and mutagenic activities (Islam et al. 2017). Moreover, a recent study suggests that Pyt is valuable to synthesize biologically active principles (Gliszczyńska et al. 2021). Chromosomal instability and DNA damage are associated with several diseases, especially cancer. Therefore, it is important to understand the mechanisms of cytogenetic abnormalities in tumorigenesis (Grade et al. 2015). Cytogenetic changes involve aneuploidy, deletions, insertions, breaks, and chromosomal losses (Giam and Rancati 2015). Testing of micronuclei with the block of cytokinesis (CBMN) can determine the levels of cytogenetic damage in binucleate cells caused by therapeutic agents (Nakamura et al. 2016). In a similar fashion, the comet assay can detect low levels of DNA damage, such as single and double strand breaks (SSBs/DSBs) (Kawaguchi et al. 2010), as well as oxidative damage (Davison 2016).

This study aimed to evaluate the anticancer effects of Pyt by cytogenetic mechanisms indicative of genotoxicity, mutagenicity, apoptosis, and necrosis in primary cultures of sarcoma 180 (S-180) and human leukemia (HL-60) cell lines using the alkaline comet assay and CBMN tests.

Materials and methods

Chemicals and reagents

Phytol (Pyt) was purchased from Sigma-Aldrich (St. Louis, MO, USA, catalog number: 139912). RPMI 1640 culture medium, penicillin, and streptomycin were obtained from GIBCO® (Invitrogen, Carlsbad, CA, USA, catalog numbers: 11875119 and 15070063, respectively). Doxorubicin (Dox) was acquired from Eurofarma Laboratories S.A. (São Paulo, Brazil, catalog number: 100430004), while hydrogen peroxide (H_2O_2) was purchased from Dynamics Química Contemporânea LTDA (São Paulo, Brazil, catalog number: 1857). Pyt was emulsified in 0.05% tween 80 (Dynamics Química Contemporânea LTDA, São Paulo, Brazil, catalog number: P.10.1089.003.00) dissolved in 0.9% saline solution to attain the test concentrations (4.72, 7.08 and 14.16 μM), whereas Dox was used in a single concentration (6 μM, solubilized in distilled H_2O). The test concentrations for this study were selected on the basis of our previous cytoprotective (Islam et al. 2016) and cytogenotoxicological (Islam et al. 2016) studies. On the other hand, the H_2O_2 solution was prepared to a final concentration of 10 mM in distilled H_2O.

Experimental animals

Adult male *Swiss* mice (weighing 25–30 g, B.W.) were collected from the Central Animal Facility of the Center for Agricultural Sciences at the Federal University of Piau (UFPI). The animals were given free access to standard food (Purina, Brazil) and water *ad libitum*. They were kept at 24 ± 2 °C under controlled lighting (12-hour dark/light cycles). This project was approved by the Ethics Committee on Animal Experimentation of the UFPI and filed under approval number 004/15.

Primary culture of sarcoma 180 (S-180) cells

S-180 cells were collected from the UFPI Cancer Lab and maintained in the peritoneal cavity of mice (UFPI, # 167/16), according to Gonzaga et al. (2009). After 10 days of inoculation, ascitic fluid containing tumor cells was removed via a puncture in the abdominal cavity of the animal. Then, the cells were counted in Neubauer's chamber (4×10^6 cells/mL), incubated in RPMI 1640 medium supplemented with 10% (v/v) fetal bovine serum and 1% (w/v) penicillin/streptomycin, and kept in an incubator at 37 °C for 72 h along with test and control substances.

Cultured human leukemia (HL-60) cells

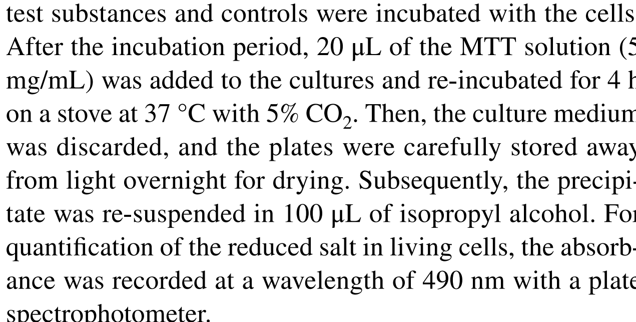
HL-60 cells were collected from the UFPI Cancer Lab and stored in liquid nitrogen until used. The cell line was thawed by the gentle shaking of its containers for 2 minutes at 37 °C in a water bath. After thawing, the contents of each container containing the cells were transferred to a culture flask and diluted with up to 10 mL of RMPI medium 1640 (1 mM/L GIBCO® L-glutamine [Invitrogen, Carlsbad, CA, USA, catalog number: 25030149] supplemented with 10% (v/v) GIBCO® fetal bovine serum [Invitrogen, Carlsbad, CA, USA, catalog number: 12657029] and 1% (w/v) penicillin/streptomycin). Culture flasks (containing 2 x 10^6 viable cells) were observed under an inverted microscope, followed by incubation in an oven at 37 °C and humidification in a 5% CO_2 atmosphere. Periodically, cultures were diluted and maintained under the same conditions at a density of 5×10^5 cells/mL and harvested at the exponential growth stage (Yedjou et al. 2010).

Cell viability test by trypan blue in S-180

A trypan blue exclusion test was employed to evaluate cell viability and determine the number of viable cells in the cell suspension according to a procedure outlined by Strober (2015). After 72 h of treatment with the test substances and controls, 90 µL of the cell suspension (0.5 x 10^6 cells/mL) was withdrawn from the cultures and added to 10 µL of trypan blue (Invitrogen, Carlsbad, CA, USA, catalog number: 15250061). Non-viable cells, considered dead cells, were identified by their bluish coloration. In contrast, viable cells do not exhibit this staining because of their ability to expel trypan blue. Light microscopy 400× was used to evaluate cellular differentiation. This was accomplished with the aid of a Neubauer chamber.

Cell viability by MTT assay in HL-60 cells

The MTT assay was performed according to the method of Mosmann (1983). Cells were distributed in 96-well multiplates at a density of 0.8 x 10^6 cells/mL. For 68 hours,


test substances and controls were incubated with the cells. After the incubation period, 20 µL of the MTT solution (5 mg/mL) was added to the cultures and re-incubated for 4 h on a stove at 37 °C with 5% CO_2. Then, the culture medium was discarded, and the plates were carefully stored away from light overnight for drying. Subsequently, the precipitate was re-suspended in 100 µL of isopropyl alcohol. For quantification of the reduced salt in living cells, the absorbance was recorded at a wavelength of 490 nm with a plate spectrophotometer.

Micronucleus test with cytokinesis block (CBMN) assay

The CBMN test was done according to the method described by Fenech (2007) and modified by de Lima et al. (2020), with minor modifications. Briefly, a 20 µL suspension of S-180 cells (0.5×10^6 cells/mL) or HI-60 cells (0.8 $\times 10^6$ cells/mL) was added to the culture flask, which contains 2 mL of RPMI 1640 medium (GIBCO® phytohemagglutinin [Invitrogen, Carlsbad, CA, USA, catalog number: 10576015], supplemented with 1 mM/L of L-glutamine, 10% (v/v) fetal bovine serum, and 1% (w/v) penicillin/streptomycin). Cells were incubated for 44 h at 37 ± 1 °C, followed by the addition of 6 µg/mL of cytochalasin B (Sigma, St. Louis, MO, catalog number: C6762). Vials were incubated for another 28 hours, then cultures were transferred to Falcon tubes and centrifuged at 800 rpm for 5 min. Then, the supernatant was removed, and the cell pellet was lightly shaken and centrifuged again after the addition of 5 mL of a fixative (5:1 methanol:acetic acid) and 3 drops of formaldehyde to the tubes. This procedure was repeated twice, using a 3:1 fixative and without formaldehyde. Finally, the supernatant was discarded, and 2–4 drops of the cell suspension were dripped onto slides, which were stained with a 5% Giemsa (Sigma, St. Louis, MO, catalog number: 48900) solution for 7 min. The previously coded slides were analyzed in a blinded test with the aid of an optical microscope (1000×), and the cytogenetic damage present in 1000 cells per slide was counted in duplicate.

Alkaline comet assay

The alkaline version of the comet assay was conducted according to the procedure described by Speit and Rothfuss (2012) and modified by de Lima et al. (2020). Briefly, 10 µL aliquots of S-180 (0.5×10^6 cells/mL) and HL-60 (0.8×10^6 cells/mL) cell suspensions were mixed with a thin layer of 0.75% low melting point agarose (90 µL) and placed on pre-coated slides with 1.5% normal melting point agarose (Sigma, St. Louis, MO, catalog numbers: A9539). Slides were dipped in a lysis solution (2.5 M NaCl, 100 mM EDTA, and 10 mM Tris, pH 10, with the addition of 1%

Triton X-100 and 10% DMSO (Sigma, St. Louis, MO, catalog numbers: S9888, ED, X100 and 276855, respectively) at the time of use) for up to 72 h at 4 °C, incubated in alkaline buffer (300 mM NaOH and 1 mM EDTA, pH >13) for 20 min, and then exposed to an electric current of 300 mA and 25 V (0.90 V/cm) for 15 min in an electrophoretic cell. At the end, slides were neutralized with Tris buffer (0.4 M and pH 7.5) and stained with a silver solution. Slides were then analyzed for the photomicrograph profile of the cells (at a magnification of 400× under an optical microscope), and the results were expressed as damage index (ID) and frequency of damage (FD) for 100 cells in duplicate. ID was calculated using the following formula: ID = Σ (number of cells in a given damage class x harm class), ranging from 0 to 400, while FD was calculated by the following formula: FD = 100–number of class 0 cells.

Hydrogen peroxide (H_2O_2)-induced genotoxicity test

This test was done according to the method described by Luz et al. (2013) and modified by de Lima et al. (2020). Briefly, 10 µL aliquots of S-180 cell suspension (0.5×10^6 cells/mL) were mixed with a thin layer of 0.75% low melting point agarose (90 µL) and placed on pre-coated slides with 1.5% normal melting point agarose. Slides were then exposed to Pyt (14.16 µM) and/or H_2O_2 (10 mM/mL) for 5 min. Slides were then dipped in a lysis solution (2.5 M NaCl, 100 mM EDTA, and 10 mM Tris (pH 10.0), with the addition of 1% Triton X-100 and 10% DMSO at the time of use) for 5 min at 4 °C. After this procedure, the comet assay was continued as discussed above.

Statistical analysis

Results are expressed as the mean ± standard deviation (SD). All determinations were conducted in duplicate, and the data were subjected to a two-way analysis of variance (ANOVA). Statistical analysis was performed using the Tukey's test for significance with the aid of the GraphPad Prism program (San Diego, CA, USA) by considering $p < 0.05$ at 95% confidence intervals.

Results

Cell viability assay

The effects of Pyt and controls on S-180 and HL-60 cell lines are presented in Fig. 1. The findings exhibited that both Pyt and Dox exert significant cytotoxic effects on the cell lines after 72 h of exposure. It produced more prominent effects against HL-60 cell lines as compared to S-180, and the overall effects were comparable to those of a standard drug. Half-minimal inhibitory concentrations (IC_{50}s) for S-180 and HL-60 cell lines were 18.98 ± 3.79 and 1.17 ± 0.34 µM, respectively.

Genotoxic effects on S-180 cells

Pyt exerted significant genotoxic effects at all tested concentrations. The overall effect was concentration-dependent with maximum damage at 14.16 µM on the S-180 cell line (Fig. 2). It was also observed that it significantly increased the index and frequency of damage as compared to untreated tumor cells.

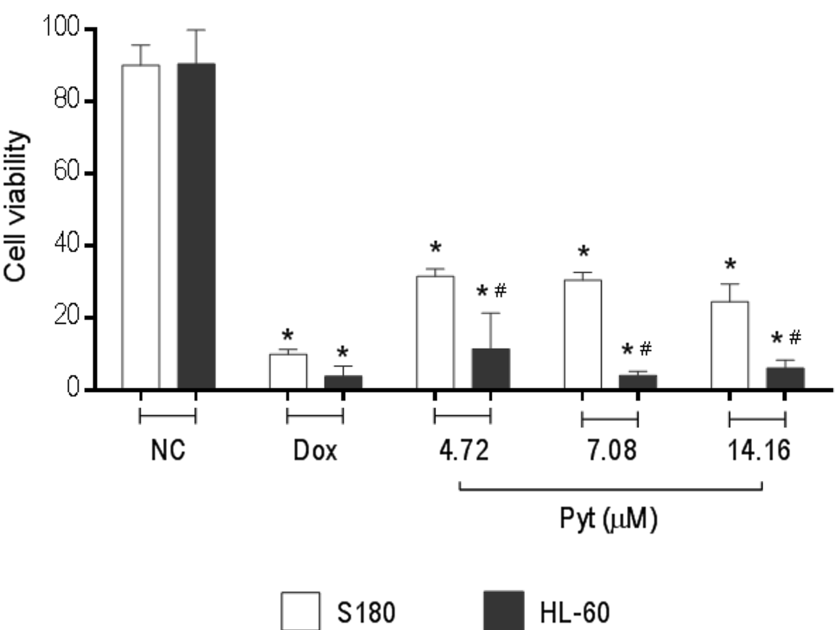


Fig. 1 Cell viability assessed by the trypan blue exclusion test in S-180 and MTT assay in HL-60 after 72 h of exposure. Values are mean ± SD, four independent experiments; ANOVA, two-way, followed by Tukey post-test at *p <0.05 compared to the NC group; #p <0.05 compared to S180 group, at the same concentration; NC: untreated cells; Dox: Doxorubicin (6 µM); Pyt: Phytol

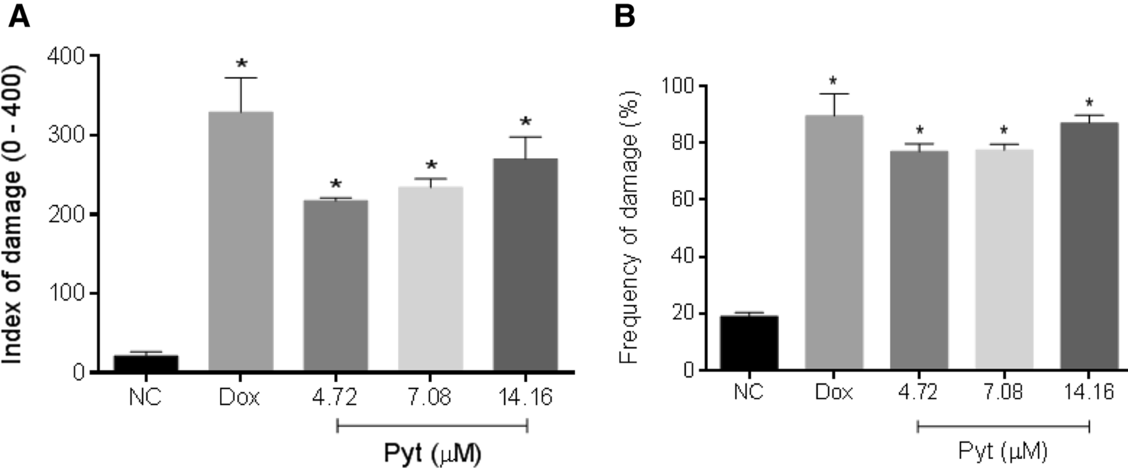


Fig. 2 Genotoxicity of phytol and doxorubicin in S-180 after 72 h of exposure. Values are mean ± SD, four independent experiments; ANOVA, two-way, followed by Tukey post-test at *p <0.05 compared to the NC group; (A) Damage index; (B) Frequency of damage; NC: Untreated cells; Dox: Doxorubicin 2 μg; Pyt: Phytol

The photomicrographs show the differences between the study groups in relation to the types (classes) of DNA damage (0, 1, 2, 3, and 4). The Pyt showed similarity of damage with the Dox-treated group, especially at 7.08 and 14.16 μM, by the frequency of types 3 and 4, indicative of apoptosis, as presented in Fig. 3.

(A) Cells without treatment; (B) Cells treated with doxorubicin 6 μM; (C and D) Cells treated with phytol 4.72 and 7.08 μM; (E and F) Cells treated with phytol 14.16 μM; T0-T4: Type 0 to type 4 damages; Ap: Apoptosis.

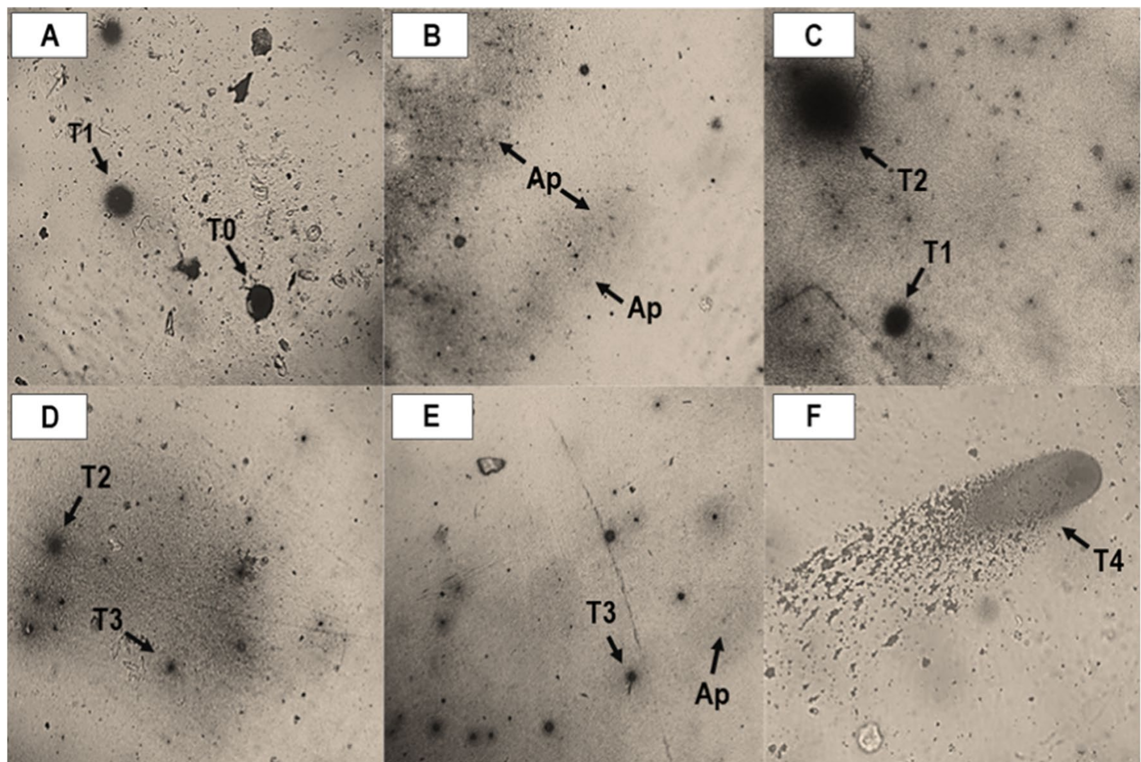


Fig. 3 Photomicrographic profile of S-180

Oxidative damage induced in S-180 cells

The effect of oxidative damage induced by Pyt in S-180 is presented in Table 1. It caused significant genotoxicity when S-180 cells were treated with Pyt with H_2O_2.

Cytogenetic effects in S-180 and HL-60 cells

Pyt at 14.16 μM increased the formation of micronuclei and showed a mutagenic effect on S-180 and HL-60 cells. It also significantly ($p < 0.05$) increased the number of nuclear bridges and shoots in a concentration-dependent manner when compared to the negative control (NC) group. The cytotoxic effects of Pyt were also observed by means of the cell division index (IDN) in a concentration-dependent fashion, as indicated by the rates of apoptosis and necrosis (Table 2 and 3, and Figs. 4 and 5).

Figure 4 shows the cytogenetic markers for the cytotoxic and antitumor effects of Pyt, such as the MN, nuclear bridges and buds, triadradial figures (trilobular nucleus), binucleate cells, apoptosis, and necrosis.

Arrows point to: (A) Necrosis, (B) Necrosis co-occurring with a triradial figure, (C) Isolated triradial figure, (D) Micronucleus, (E) Apoptotic cell, (F) Nucleoplasmic bridge.

Table 1 Oxidative stress-induced genotoxic effects of phytol and/or controls in S-180 co-treated with H_2O_2

Parameters	Groups			
	NC	H_2O_2	Pyt	Pyt + H_2O_2
ID (0 - 400)	40.7 ± 7.80	178.0 ± 2.44*	166.3 ± 23.34*	164.3 ± 18.52*
FD (%)	61.5 ± 5.91	97.7 ± 0.95*	95.5 ± 2.63*	96.7 ± 1.89*

Values are mean ± SD of four independent experiments. NC: Untreated cells. H_2O_2: Hydrogen peroxide (10 mM). Pyt: Phytol (14.16 μM). ANOVA, one-way, followed by Tukey post-test. *$p < 0.05$ compared to the CN group

Table 2 Cytogenetic damage profiles in phytol and control groups in S-180 after 72 h of exposure (CBMN test)

Treatments S180	Cytogenetic damages			Cytotoxicity	
	MN	Bridges	Buds	IDN	IDNC
NC	1.75 ± 1.02	2.80 ± 0.41	1.70 ± 0.12	1.69 ± 0.037	1.60 ± 0.033
Dox	36.50 ± 0.35[a]	35.5 ± 3.53[a]	17.0 ± 1.41[a]	1.11 ± 0.04[a]	1.23 ± 0.007[a]
Pyt 4.72 μM	8.00 ± 0.70	5.55 ± 2.12	2.00 ± 1.41	1.40 ± 0.018	1.26 ± 0.062
Pyt 7.08 μM	10.70± 1.76	8.50 ± 2.25[a]	11.0 ± 1.82[a]	1.35 ± 0.281	1.19 ± 0.146[a]
Pyt 14.16 μM	29.70 ± 3.18[a]	27.00 ± 7.04[abc]	28.50 ± 2.12[a]	1.25 ± 0.054[a]	1.16 ± 0.032[a]

Values are mean ± SD of four independent experiments. NC: Untreated cells. Dox: Doxorubicin 2 μg. Pyt: Phytol. MN: Micronucleus. IDN: Nuclear division index. IDNC: Nuclear division index considering apoptosis and necrosis. ANOVA, one-way, followed by Tukey post-test. [a]$p < 0.05$ compared to the NC, [b]$p < 0.05$ compared to the Pyt 4.72. [c]$p < 0.05$ compared to the Pyt 7.08

Table 3 Cytogenetic damage caused by phytol and control groups in HL-60 after 72 h of exposure (CBMN test)

Treatments HL-60	Cytogenetic damages			Cytotoxicity	
	MN	Bridges	Buds	IDN	IDNC
NC	2.00 ± 1.41	2.50 ± 0.70	1.50 ± 0.70	1.73 ± 0.03	1.64 ± 0.004
Dox	28.0 ± 11.3[a]	41.5 ± 7.77[a]	26.00 ± 2.80[a]	1.07 ± 0.002[a]	1.16 ± 0.007[a]
Pyt 4.72 μM	9.50 ± 3.53	13.0 ± 1.41	11.00 ± 2.42	1.55 ± 0.12	1.36 ± 0.14
Pyt 7.08 μM	12.50 ± 3.45[a]	19.5 ± 2.21	25.00 ± 4.23	1.30 ± 0.08	1.24 ± 0.07[a]
Pyt 14.16 μM	26.00 ± 5.65[a]	39.0 ± 5.65[a]	28.50 ± 2.12[a]	1.33 ± 0.12	1.24 ± 0.05[a]

Values are mean ± SD of four independent experiments. NC: Untreated cells. Dox: Doxorubicin 2 μg. Pyt: Phytol. MN: Micronucleus. IDN: Nuclear division index. IDNC: Nuclear division index considering apoptosis and necrosis. ANOVA, one-way, followed by Tukey post-test. [a]$p < 0.05$ compared to the NC group

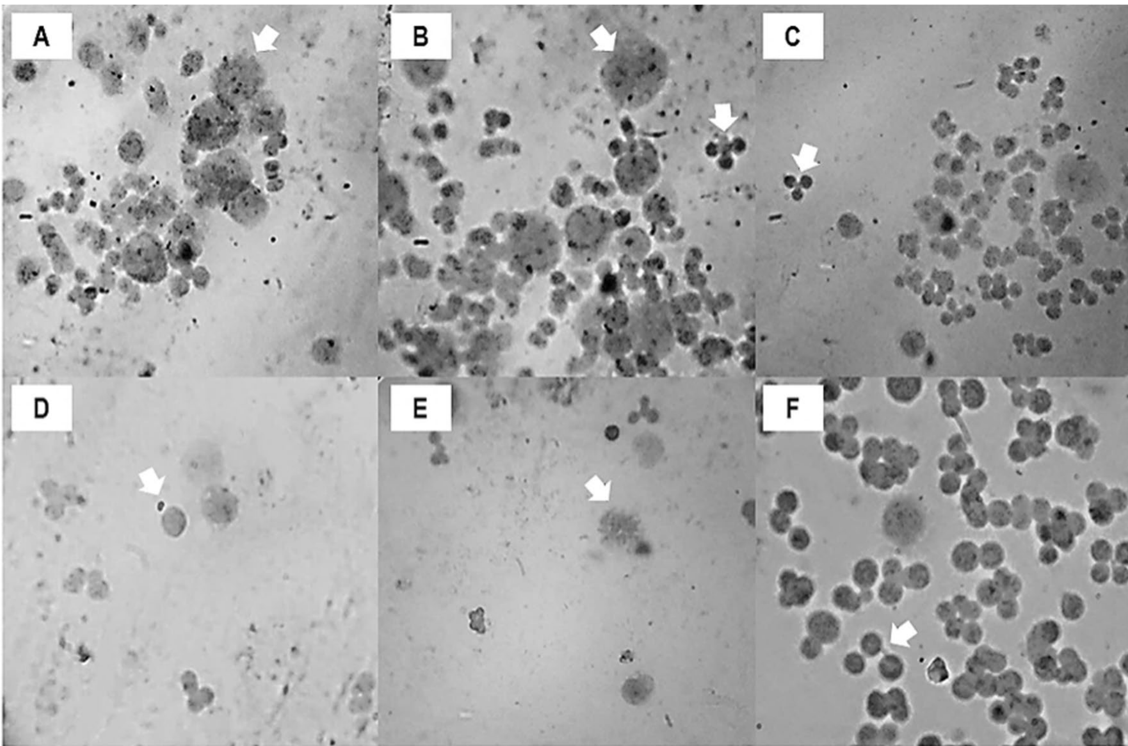


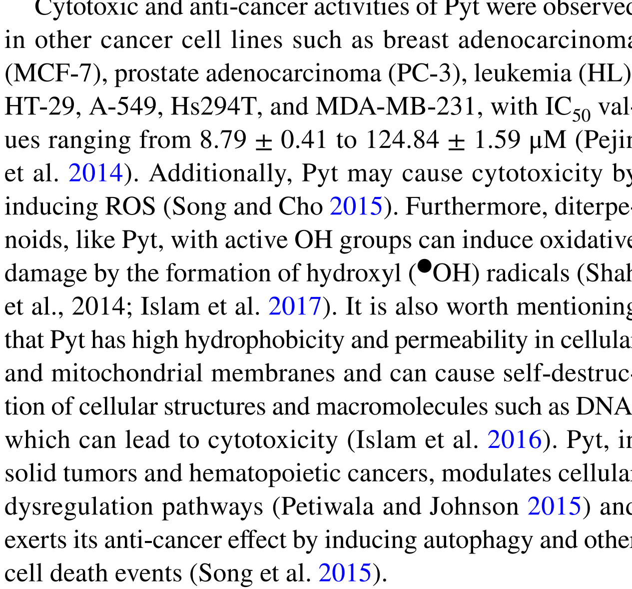
Fig. 4 Photomicrographic profile of HL-60 treated with phytol 14.16 µM in the CBMN test

Apoptosis and necrosis effects in S-180 and HL-60 cells

As shown in tables 2 and 3 and in Figs. 6 A and B, the results of our study pertaining to apoptosis and necrosis caused by Pyt in S-180 and HL-60 cells were evaluated by the CBMN test. Our findings reveal that Pyt at all tested concentrations significantly increased the number of apoptosis (Fig. 6 A) and necrosis (Fig. 6 B) at 14.16 µM compared to the NC group, indicating a cytotoxic action on S-180 cells; similar results were also observed in the HL-60 cell line. It should be noted that differences were observed between the effects of Pyt and the standard anti-neoplastic drug Dox (Fig. 6 A and B).

Discussion

Natural products and their derivatives have historically been a valuable source of therapeutic agents (Dey et al. 2016). In this context, terpenoids are cytotoxic to tumor cells and thus can be used as chemotherapeutic or chemo-preventive agents and as adjuvants in cancer therapies (Ghosh 2012). Our findings in this study show that Pyt can induce cytotoxicity in S-180 and HL-60 cell lines by inhibiting cell viability in the blue trypan and MTT assays. Cytotoxic drugs may inhibit cell viability through mechanisms associated with cell cycle trimming and the induction of apoptosis (Tajudin et al. 2012).



Cytotoxic and anti-cancer activities of Pyt were observed in other cancer cell lines such as breast adenocarcinoma (MCF-7), prostate adenocarcinoma (PC-3), leukemia (HL), HT-29, A-549, Hs294T, and MDA-MB-231, with IC_{50} values ranging from 8.79 ± 0.41 to 124.84 ± 1.59 µM (Pejin et al. 2014). Additionally, Pyt may cause cytotoxicity by inducing ROS (Song and Cho 2015). Furthermore, diterpenoids, like Pyt, with active OH groups can induce oxidative damage by the formation of hydroxyl (●OH) radicals (Shah et al., 2014; Islam et al. 2017). It is also worth mentioning that Pyt has high hydrophobicity and permeability in cellular and mitochondrial membranes and can cause self-destruction of cellular structures and macromolecules such as DNA, which can lead to cytotoxicity (Islam et al. 2016). Pyt, in solid tumors and hematopoietic cancers, modulates cellular dysregulation pathways (Petiwala and Johnson 2015) and exerts its anti-cancer effect by inducing autophagy and other cell death events (Song et al. 2015).

Published research showed that Pyt exhibited concentration-dependent cytotoxic activity in MCF-7 and PC-3 cell lines, which may suggest its usage for the manufacture of anti-cancer drugs (NCI 2014). In a recent study, it exerted anti-cancer effects on RAW264.7 cells via suppressing osteoclast differentiation and oxidative stress through the nuclear factor erythroid 2–related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway (Kim et al. 2022). In addition, due to its cytotoxicity, it can also be a candidate for the design of new

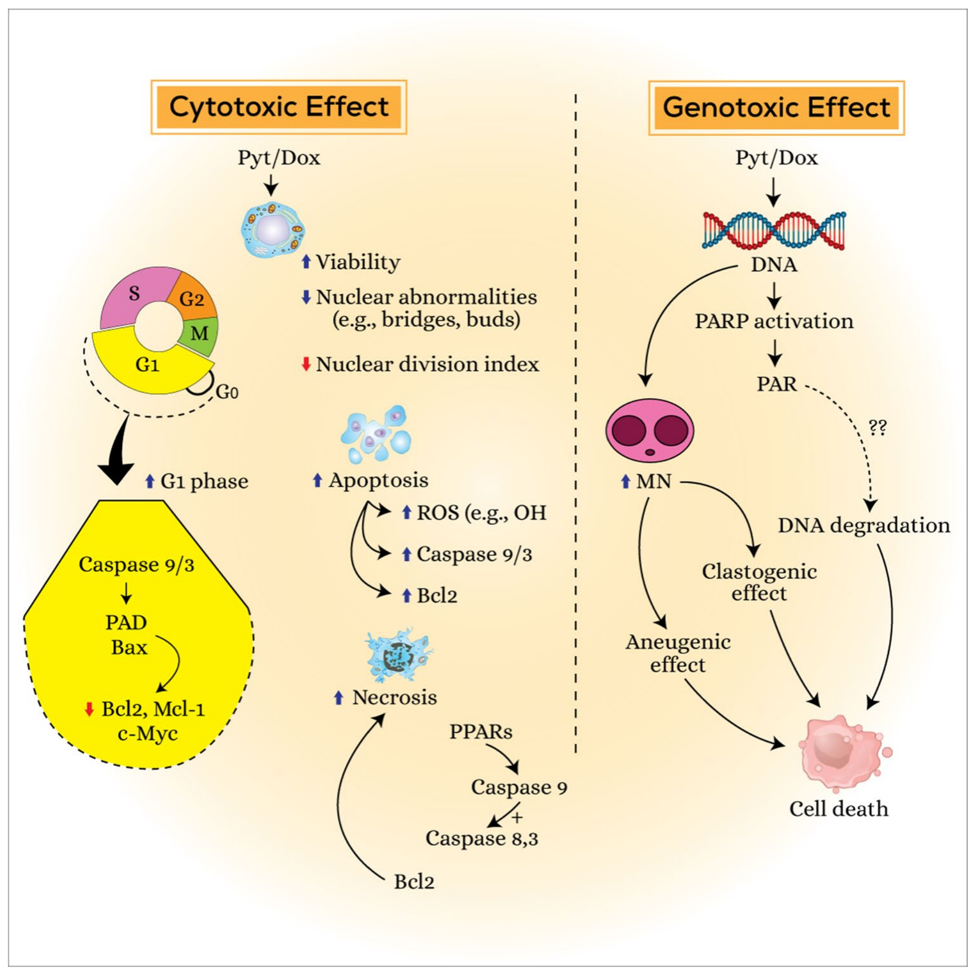
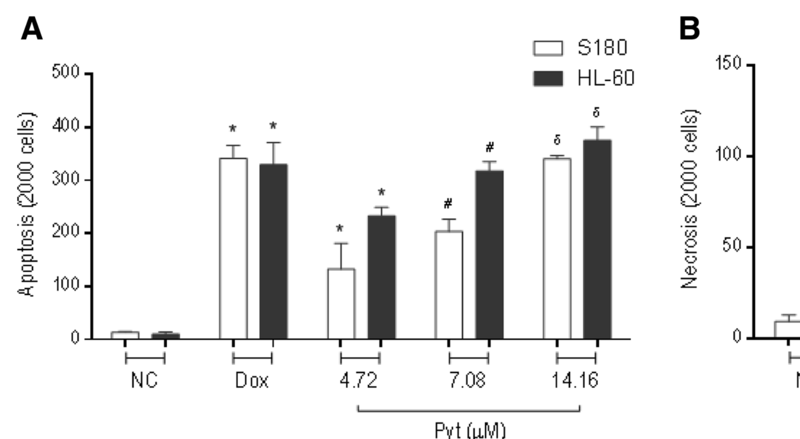


Fig. 5 Possible cytogenotoxic effect mechanism of phytol in the test systems



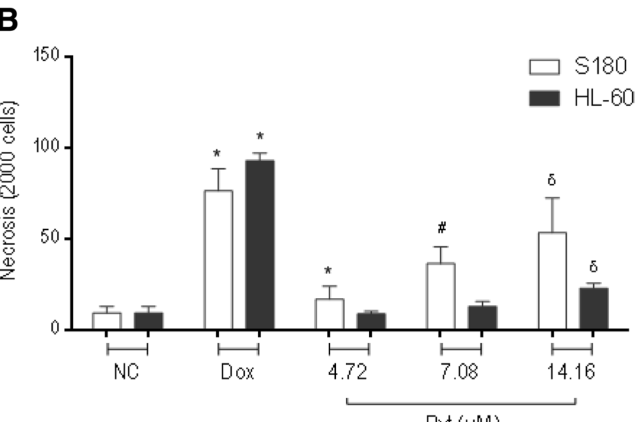


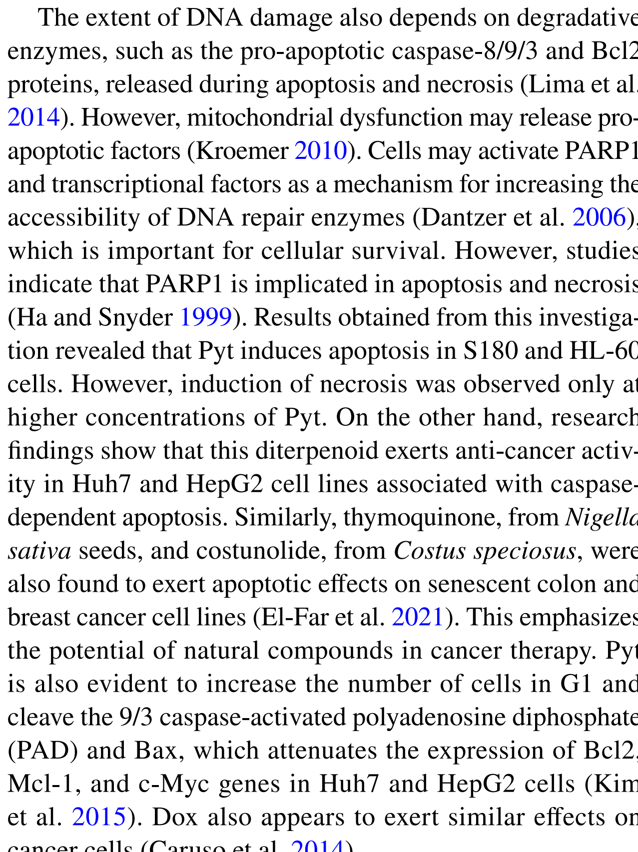
Fig. 6 Apoptosis and necrosis induced by phytol in S-180 and HL-60 cell lines after 72 h of exposure. [(A) Apoptosis; (B) Necrosis; Values are mean ± SD, four independent experiments; ANOVA, two-way, followed by Tukey post-test. *p <0.05 compared to the NC; #p <0.05 compared to the NC and Pyt 4.72; δp <0.05 compared to the NC and Pyt 4.72 and Pyt 7.08 μM; NC: Untreated cells; Dox: Doxorubicin 6 μM; Pyt: Phytol]

drugs, considering the selectivity of this diterpenoid (Pejin et al. 2014). On the other hand, genetic toxicity analysis can be performed by means of the *in vitro* and *ex vivo* comet assay for assessment of DNA damage and DNA repair capability (Pourrut et al. 2015), and in its alkaline version, it can detect SSBs and/or DSBs, alkali-labile sites, and oxidative

damage (Davison 2016). In genotoxicity analysis, Pyt, at all concentrations, induced an increase in the ID and FD in S-180. It caused similar genotoxicity in S-180 as compared to H_2O_2, as it could generate $^{\bullet}OH$ (Islam et al. 2016). Pyt can also increase the levels of thiobarbituric acid substances (TBARS), cause lipid peroxidation, and cause a decrease in glutathione (GSH) enzymes (Leipnitz et al. 2010).

In HepG2 cells and using the luciferase activity assay, results from this study showed that Pyt directly activates peroxisome proliferator-activated receptors (PPARs) and indirectly through its phytaneic acid metabolite (FA) (Goto et al. 2005). FA inhibits histone deacetylase (Hdac2) and induces cell death, with cytotoxic effects associated with caspase-9, as observed in neuronal cells (Nagai 2015), as well as generate free radicals during β-oxidation (Tamatani et al. 1999), causing oxidative stress with potential DNA damage (Stadelmann-Ingrand et al. 2004). On the other hand, depolymerase inhibitors (ADP-ribose)-polymerase (PARP), such as it, cause DNA damage and may inhibit repair pathways such as base excision repair (BER), and therefore are considered promising as antineoplastic drugs (Velic et al. 2015).

Genotoxic damage with higher intensity triggers unrepaired genomic instability coupled with extensive genotoxicity, which at the chromosomal/molecular level can cause mutations in DNA (Zhang et al. 2014). This may be due to the ability of chromosomal damage, rearrangement, nondisjunction, gene amplification, necrosis, and apoptosis to result in the formation of MN (mainly from chromosomal fragments or whole chromosomes that fail to be directed to the mitotic spindle when the cell divides) (Bhatia and Kumar 2013). Chromosomal instability contributes to human neoplasms through chromosome malsegregation, aneuploidy, damage to DNA, mutations, and chromosome translocations. An earlier study indicated that these chromosomal alterations may contribute to the formation of MN, which may be important for cancer therapy (Bakhoum and Compton 2012). In this study, Pyt induced mutagenicity by initiating nuclear MN bridges and buds in S-180 and HL-60 cells, especially at the highest concentrations tested, leading to cytotoxicity determined by IDN. The increase in MN frequency is associated with deficiencies in DNA damage responses. MN represents fragmentation and/or loss of whole chromosomes (Maluf and Erdtmann 2001). In addition, they are markers to detect clastogenic and aneugenic agents in genotoxic and mutagenic compounds (Kirsch-Volders et al. 2011). Nucleoplasmic bridges are derived from chromosomal rearrangements and fusion of telomeres (Fenech 2000), and the nuclear buds represent DNA amplification, in which telomerase has an important role in this cytogenetic alteration (Fenech et al. 2011). Manifestations of gene amplification are associated with malignant phenotypes and may arise during the cell cycle from extra-chromosomal material (Shimizu 2009).



The extent of DNA damage also depends on degradative enzymes, such as the pro-apoptotic caspase-8/9/3 and Bcl2 proteins, released during apoptosis and necrosis (Lima et al. 2014). However, mitochondrial dysfunction may release pro-apoptotic factors (Kroemer 2010). Cells may activate PARP1 and transcriptional factors as a mechanism for increasing the accessibility of DNA repair enzymes (Dantzer et al. 2006), which is important for cellular survival. However, studies indicate that PARP1 is implicated in apoptosis and necrosis (Ha and Snyder 1999). Results obtained from this investigation revealed that Pyt induces apoptosis in S180 and HL-60 cells. However, induction of necrosis was observed only at higher concentrations of Pyt. On the other hand, research findings show that this diterpenoid exerts anti-cancer activity in Huh7 and HepG2 cell lines associated with caspase-dependent apoptosis. Similarly, thymoquinone, from *Nigella sativa* seeds, and costunolide, from *Costus speciosus*, were also found to exert apoptotic effects on senescent colon and breast cancer cell lines (El-Far et al. 2021). This emphasizes the potential of natural compounds in cancer therapy. Pyt is also evident to increase the number of cells in G1 and cleave the 9/3 caspase-activated polyadenosine diphosphate (PAD) and Bax, which attenuates the expression of Bcl2, Mcl-1, and c-Myc genes in Huh7 and HepG2 cells (Kim et al. 2015). Dox also appears to exert similar effects on cancer cells (Caruso et al. 2014).

Polyphenols, especially tannins and flavonoids, may have chemo-preventive and anti-tumor properties (Zhao et al. 2015). This is further supported by studies indicating the anticancer potential of other compounds like the antimetabolite pemetrexed and the herbal polyphenol honokiol, which, when co-delivered using a novel self-assembled nanogel comprising natural polysaccharides and functional proteins, showed superior *in vitro* cytotoxicity (Atallah et al. 2022). Studies indicated the anti-cancer potential of terpenoids isolated from spleen oils in MCF-7 cells (wild-type p53) and MDA-MB-231 cells by inhibiting cell viability and proliferation and by inducing apoptosis with less cytotoxic effects in non-tumor cells. In both cell lines, apoptosis can be induced by activation of caspase-8/9 and cleavage of the PARP protein (Santha et al. 2013). In this context, Pyt induces apoptosis in AGS gastric adenocarcinoma cells, as indicated by the increase of cells in the sub-G1 mitotic phase, low Bcl-2 regulation, Bax overexpression, 9/3 caspase activation, PARP cleavage, mitochondrial membrane depolarization, induction of autophagy and cytotoxicity by the generation of ROS, and decreased expression of the p62 gene (Song and Cho 2015). Pyt also inhibits MB-231 tumor cells in a concentration-dependent manner, especially at 1 μM, and induces autophagy by increasing organelles with acidic enzymes (Song et al. 2015).

It should be emphasized that necrosis is also modulated by PARP1 *via the* induction of DNA damage. Some studies

suggest that this protein mediates cell death (Bredholt et al. 2015). These mechanisms are also reported for Dox, including increased mitochondrial respiration, induction of DNA damage *via* ROS, generation of nitric oxide with a decrease in PARP1, and changes in the cell cycle. However, Dox did not inhibit p53, suggesting that the anti-neoplastic-induced PARP1-dependent necrosis was independent of the *TP53* gene (Shin et al. 2015).

Conclusions

Pyt, especially at the two highest concentrations (7.08 and 14.16 μM), induced cytotoxic as well as anti-cancer effects in S-180 and HL-60 cell lines similar to those of Dox. The anticancer effect of Pyt was observed by the following different cytogenetic mechanisms: (1) induction of cytotoxicity by reduction of cell viability, interference with the free nuclear division index, and consideration of apoptosis and necrosis (2) induction of genotoxicity, possibly *via* induction of oxidative stress (3) clastogenic and/or aneugenic effects by induction of MN (4) nuclear abnormalities indicating cytotoxicity by increasing the nuclear bridges and buds; and (6) induction of apoptosis and necrosis. Pyt may be an important alternative chemotherapeutic agent.

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Data availability Not appilcable

Declarations

Conflicts of interest None declared.

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Consent to participate Not applicable

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Competing interests The authors declared no competing interest.

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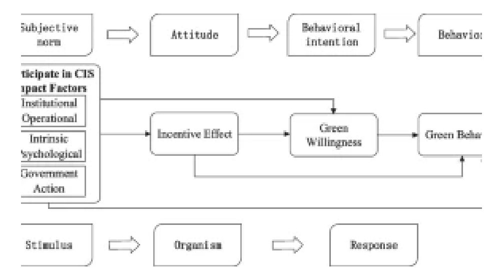

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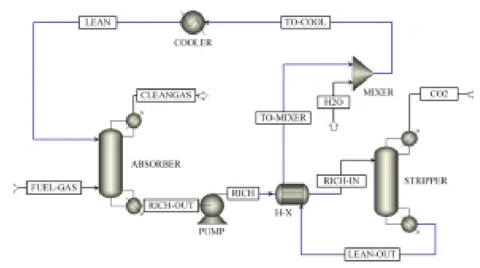

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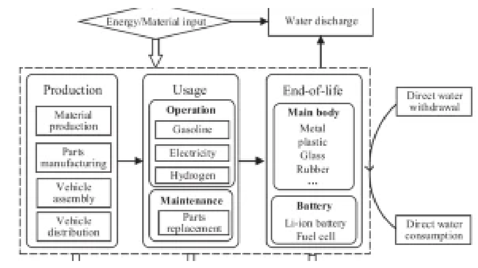

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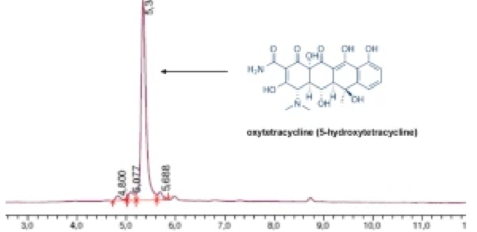

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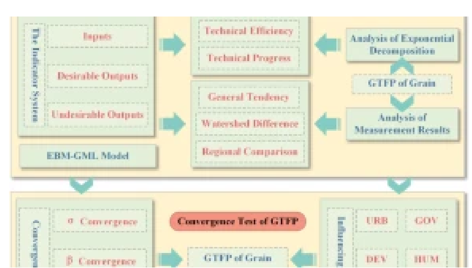

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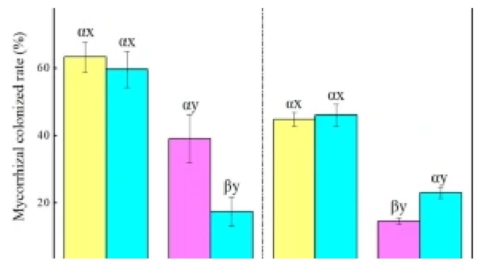

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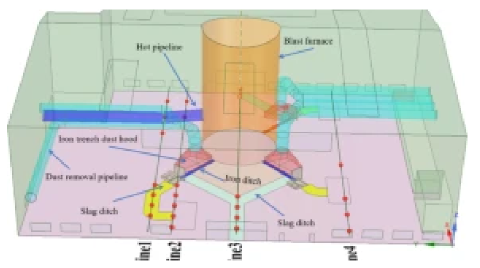

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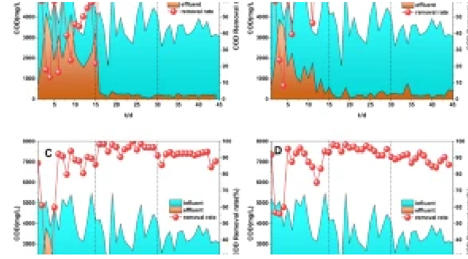

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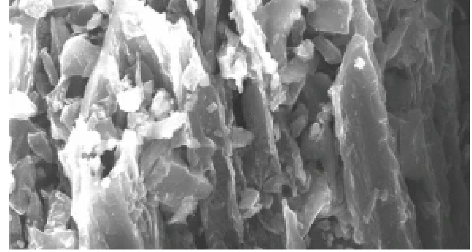

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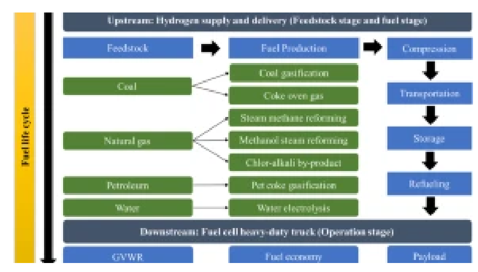

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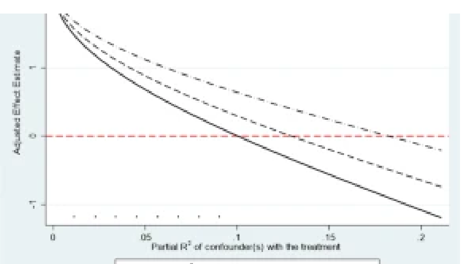

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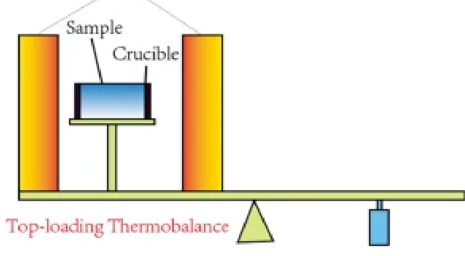

Proteogenomics of the novel *Dehalobacterium formicoaceticum* strain EZ94 highlights a key role of methyltransferases during anaerobic dichloromethane degradation

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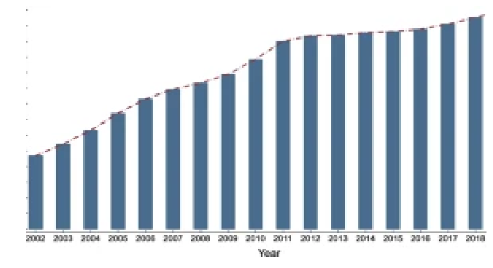
The impact of health expenditure and economic growth on CO_2 in China: a quantile regression model approach



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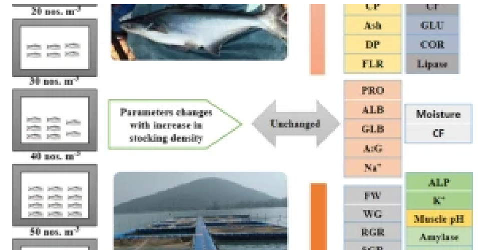

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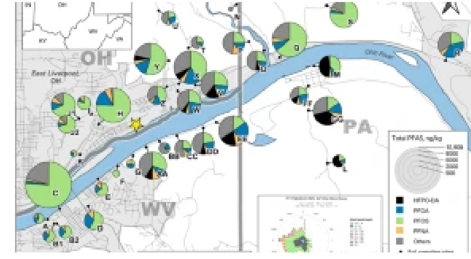

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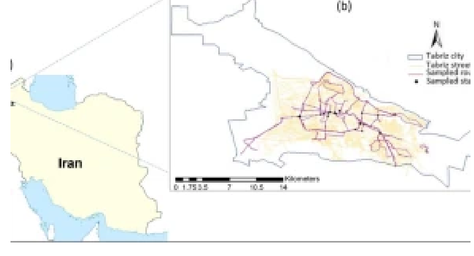

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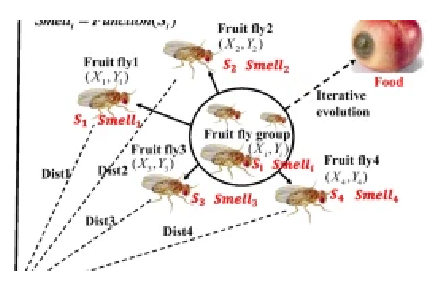

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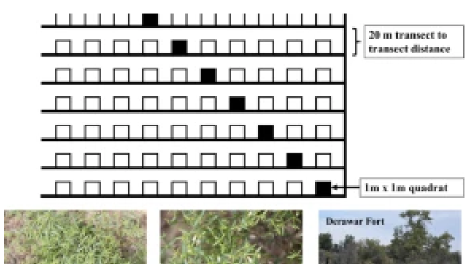

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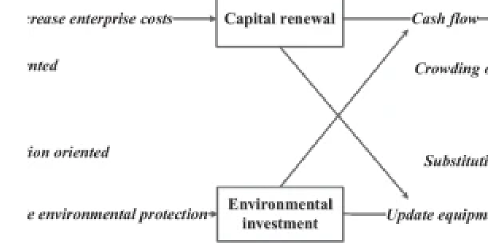

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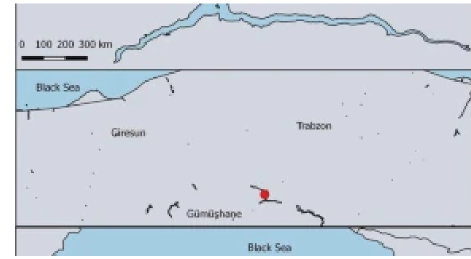

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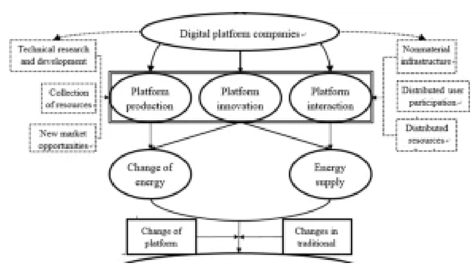

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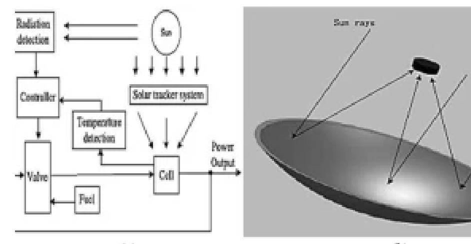

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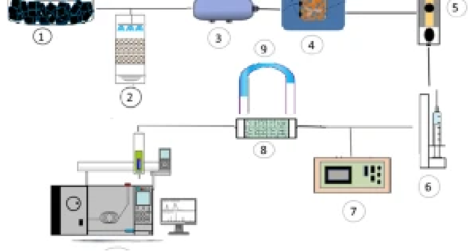

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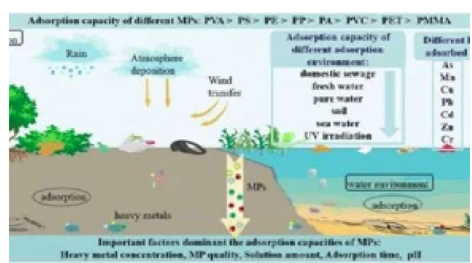

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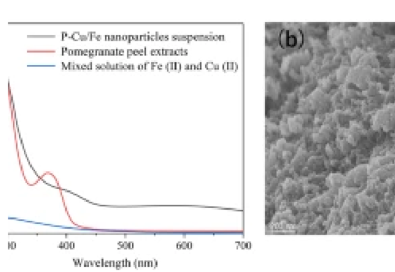

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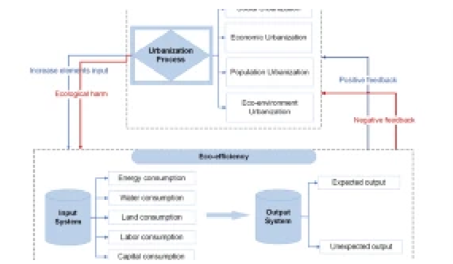

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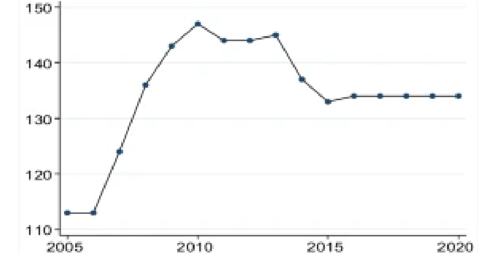

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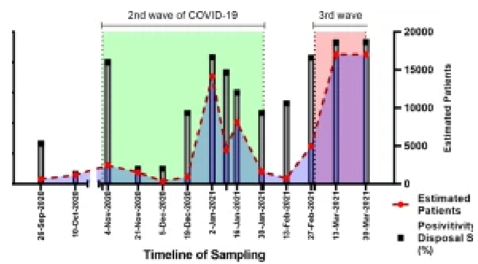

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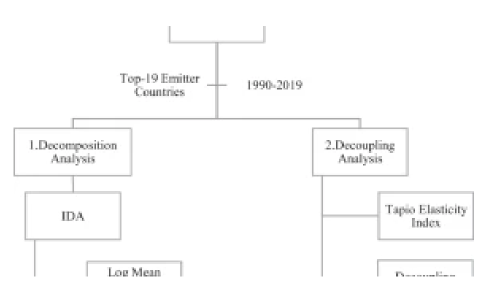

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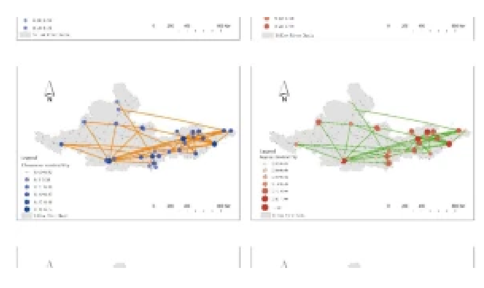

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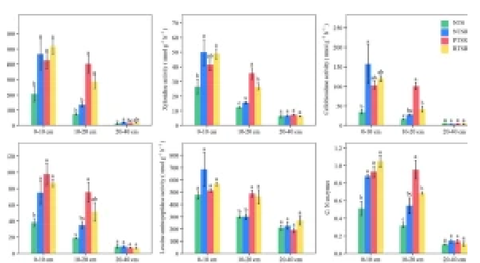

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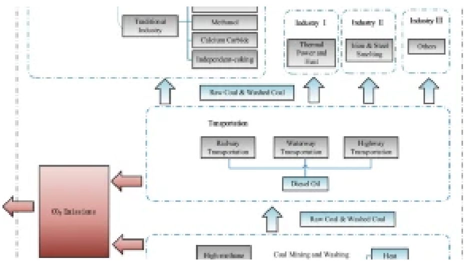

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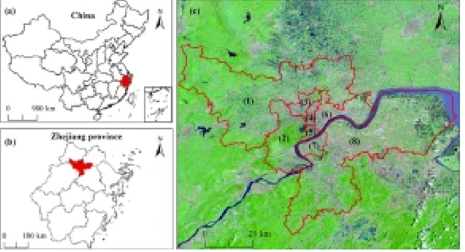

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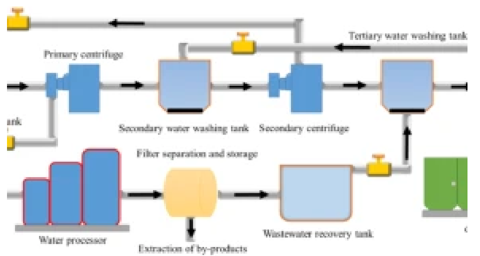

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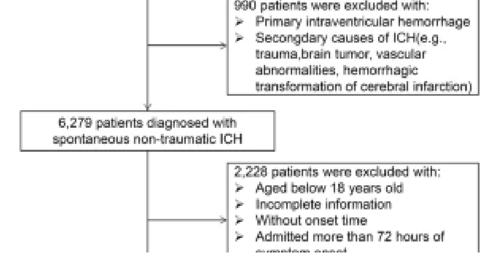

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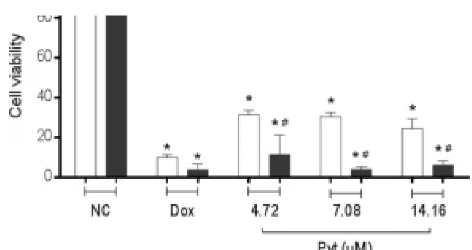

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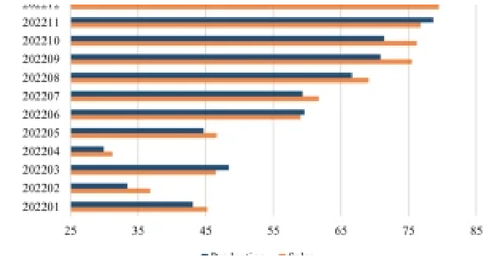

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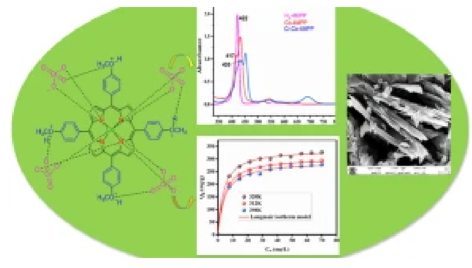

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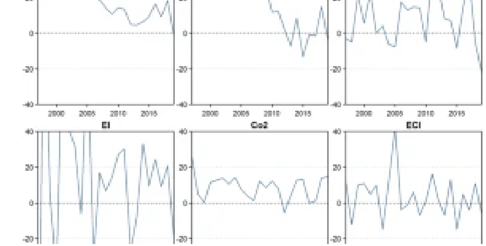

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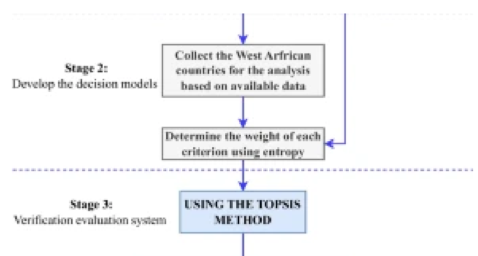

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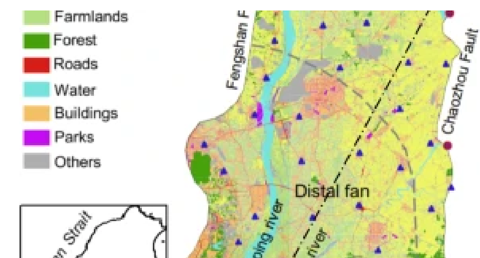

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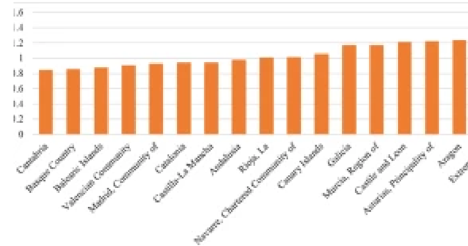

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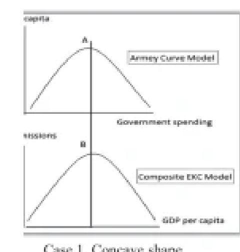

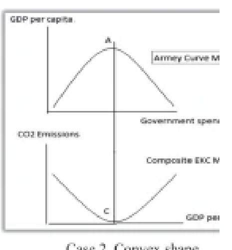

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RESEARCH ARTICLE

Anticancer effects of phytol against Sarcoma (S-180) and Human Leukemic (HL-60) cancer cells

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Abstract
Phytol (Pyt), a diterpenoid, possesses many important bioactivities. This study evaluates the anticancer effects of Pyt on sarcoma 180 (S-180) and human leukemia (HL-60) cell lines. For this purpose, cells were treated with Pyt (4.72, 7.08, or 14.16 μM) and a cell viability assay was performed. Additionally, the alkaline comet assay and micronucleus test with cytokinesis were also performed using doxorubicin (6 μM) and hydrogen peroxide (10 mM) as positive controls and stressors, respectively. Results revealed that Pyt significantly reduced the viability and rate of division in S-180 and HL-60 cells with IC_{50} values of 18.98 ± 3.79 and 1.17 ± 0.34 μM, respectively. Pyt at 14.16 μM exerted aneugenic and/or clastogenic effects in S-180 and HL-60 cells, where the number of micronuclei and other nuclear abnormalities (e.g., nucleoplasmic bridges and nuclear buds) were frequently observed. Moreover, Pyt at all concentrations induced apoptosis and showed necrosis at 14.16 μM, suggesting its anticancer effects on the tested cancer cell lines. Taken together, Pyt showed promising anticancer effects, possibly through inducing apoptosis and necrosis mechanisms, and it exerted aneugenic and/or clastogenic effects on the S-180 and HL-60 cell lines.

Keywords Phytol · Diterpenoid · Cancer cell lines · Anticancer effects

Introduction

Still, cancer remains one of the most fearful diseases worldwide, with a complex etiology that involves several biochemical, physiological, and molecular mechanisms

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(Zhang et al. 2020). Sarcomas are heterogeneous malignancies of mesenchymal origin that can occur in various tissues, such as osteosarcomas, rhabdomyosarcomas, and liposarcomas. Molecular mechanisms involved in the disease, investigated in different models, contribute to the advancement of therapies for these neoplasias (Post 2012). Generally, complex sarcomas involve multiple structural and numerical chromosomal changes, especially in epithelial sarcomas. Therefore, research is needed to elucidate cytogenetic damage (Taylor et al. 2011).

Similarly, leukemias are hematopoietic disorders that also require biological and molecular understanding, which can be studied in human cell lines such as HL-60 in the search for new natural compounds with anticancer effects (Chien et al. 2017). In this regard, it should be emphasized that there are similarities between rodents and humans regarding biological behavior and response to therapy and cytotoxic agents (Cekanova and Rathore 2014). On the other hand, drug development is still a challenge for oncology therapy due to several aspects, including the genetic heterogeneity of cancer that leads to resistance to therapies (Samadi et al. 2015).

Several studies indicate that a number of phytochemicals exhibit anti-cancer activities *via* induction of apoptosis and inhibition of cancer cell proliferation (Wu et al. 2017). To date, a number of diterpenes and their derivatives, such as manool extracted from *Salvia officinalis* (Nicolella et al. 2014), paclitaxel (Turkez et al. 2010), 7,15-trien-3-oic acid (Di Sotto et al. 2012), and taxodione (Kuźma et al. 2016), have been found to exhibit cytotoxic and genotoxic activities in different test systems. Phytol (Pyt) (3,7,11,15-tetramethyl-1-hexadecene-2-ol) is a diterpenoid with various pharmacological effects (Islam et al. 2015, 2016, 2018). Scientific reports suggest that it possesses antispasmodic (Pongprayoon et al. 1992), non-mutagenic (Kagoura et al. 1993), anti-teratogenic (Arnhold et al. 2002), antimicrobial (Inoue et al. 2005), immunoadjuvant (Lim et al. 2006), antiepileptic (Costa et al. 2012), antiprotozoal (Bero et al. 2013), anti-inflammatory (Silva et al. 2014), antioxidant (Islam et al. 2016), antidiabetic (Elmazar et al. 2013), hypolipidemic, antinociceptive (Santos et al. 2013), antipyretic (Islam 2019), antidepressive (Costa et al. 2011), as well as cytogenotoxic and mutagenic activities (Islam et al. 2017). Moreover, a recent study suggests that Pyt is valuable to synthesize biologically active principles (Gliszczyńska et al. 2021). Chromosomal instability and DNA damage are associated with several diseases, especially cancer. Therefore, it is important to understand the mechanisms of cytogenetic abnormalities in tumorigenesis (Grade et al. 2015). Cytogenetic changes involve aneuploidy, deletions, insertions, breaks, and chromosomal losses (Giam and Rancati 2015). Testing of micronuclei with the block of cytokinesis (CBMN) can determine the levels of cytogenetic damage in binucleate cells caused by therapeutic agents (Nakamura et al. 2016). In a similar fashion, the comet assay can detect low levels of DNA damage, such as single and double strand breaks (SSBs/DSBs) (Kawaguchi et al. 2010), as well as oxidative damage (Davison 2016).

This study aimed to evaluate the anticancer effects of Pyt by cytogenetic mechanisms indicative of genotoxicity, mutagenicity, apoptosis, and necrosis in primary cultures of sarcoma 180 (S-180) and human leukemia (HL-60) cell lines using the alkaline comet assay and CBMN tests.

Materials and methods

Chemicals and reagents

Phytol (Pyt) was purchased from Sigma-Aldrich (St. Louis, MO, USA, catalog number: 139912). RPMI 1640 culture medium, penicillin, and streptomycin were obtained from GIBCO® (Invitrogen, Carlsbad, CA, USA, catalog numbers: 11875119 and 15070063, respectively). Doxorubicin (Dox) was acquired from Eurofarma Laboratories S.A. (São Paulo, Brazil, catalog number: 100430004), while hydrogen peroxide (H_2O_2) was purchased from Dynamics Química Contemporânea LTDA (São Paulo, Brazil, catalog number: 1857). Pyt was emulsified in 0.05% tween 80 (Dynamics Química Contemporânea LTDA, São Paulo, Brazil, catalog number: P.10.1089.003.00) dissolved in 0.9% saline solution to attain the test concentrations (4.72, 7.08 and 14.16 μM), whereas Dox was used in a single concentration (6 μM, solubilized in distilled H_2O). The test concentrations for this study were selected on the basis of our previous cytoprotective (Islam et al. 2016) and cytogenotoxicological (Islam et al. 2016) studies. On the other hand, the H_2O_2 solution was prepared to a final concentration of 10 mM in distilled H_2O.

Experimental animals

Adult male *Swiss* mice (weighing 25–30 g, B.W.) were collected from the Central Animal Facility of the Center for Agricultural Sciences at the Federal University of Piau (UFPI). The animals were given free access to standard food (Purina, Brazil) and water *ad libitum*. They were kept at 24 ± 2 °C under controlled lighting (12-hour dark/light cycles). This project was approved by the Ethics Committee on Animal Experimentation of the UFPI and filed under approval number 004/15.

Primary culture of sarcoma 180 (S-180) cells

S-180 cells were collected from the UFPI Cancer Lab and maintained in the peritoneal cavity of mice (UFPI, # 167/16), according to Gonzaga et al. (2009). After 10 days of inoculation, ascitic fluid containing tumor cells was removed via a puncture in the abdominal cavity of the animal. Then, the cells were counted in Neubauer's chamber (4×10^6 cells/mL), incubated in RPMI 1640 medium supplemented with 10% (v/v) fetal bovine serum and 1% (w/v) penicillin/streptomycin, and kept in an incubator at 37 °C for 72 h along with test and control substances.

Cultured human leukemia (HL-60) cells

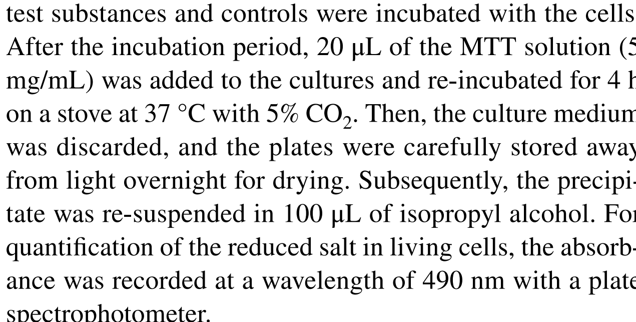
HL-60 cells were collected from the UFPI Cancer Lab and stored in liquid nitrogen until used. The cell line was thawed by the gentle shaking of its containers for 2 minutes at 37 °C in a water bath. After thawing, the contents of each container containing the cells were transferred to a culture flask and diluted with up to 10 mL of RMPI medium 1640 (1 mM/L GIBCO® L-glutamine [Invitrogen, Carlsbad, CA, USA, catalog number: 25030149] supplemented with 10% (v/v) GIBCO® fetal bovine serum [Invitrogen, Carlsbad, CA, USA, catalog number: 12657029] and 1% (w/v) penicillin/streptomycin). Culture flasks (containing 2 x 10^6 viable cells) were observed under an inverted microscope, followed by incubation in an oven at 37 °C and humidification in a 5% CO_2 atmosphere. Periodically, cultures were diluted and maintained under the same conditions at a density of 5×10^5 cells/mL and harvested at the exponential growth stage (Yedjou et al. 2010).

Cell viability test by trypan blue in S-180

A trypan blue exclusion test was employed to evaluate cell viability and determine the number of viable cells in the cell suspension according to a procedure outlined by Strober (2015). After 72 h of treatment with the test substances and controls, 90 µL of the cell suspension (0.5 x 10^6 cells/mL) was withdrawn from the cultures and added to 10 µL of trypan blue (Invitrogen, Carlsbad, CA, USA, catalog number: 15250061). Non-viable cells, considered dead cells, were identified by their bluish coloration. In contrast, viable cells do not exhibit this staining because of their ability to expel trypan blue. Light microscopy 400× was used to evaluate cellular differentiation. This was accomplished with the aid of a Neubauer chamber.

Cell viability by MTT assay in HL-60 cells

The MTT assay was performed according to the method of Mosmann (1983). Cells were distributed in 96-well multiplates at a density of 0.8 x 10^6 cells/mL. For 68 hours,



test substances and controls were incubated with the cells. After the incubation period, 20 µL of the MTT solution (5 mg/mL) was added to the cultures and re-incubated for 4 h on a stove at 37 °C with 5% CO_2. Then, the culture medium was discarded, and the plates were carefully stored away from light overnight for drying. Subsequently, the precipitate was re-suspended in 100 µL of isopropyl alcohol. For quantification of the reduced salt in living cells, the absorbance was recorded at a wavelength of 490 nm with a plate spectrophotometer.

Micronucleus test with cytokinesis block (CBMN) assay

The CBMN test was done according to the method described by Fenech (2007) and modified by de Lima et al. (2020), with minor modifications. Briefly, a 20 µL suspension of S-180 cells (0.5×10^6 cells/mL) or HI-60 cells (0.8 $\times 10^6$ cells/mL) was added to the culture flask, which contains 2 mL of RPMI 1640 medium (GIBCO® phytohemagglutinin [Invitrogen, Carlsbad, CA, USA, catalog number: 10576015], supplemented with 1 mM/L of L-glutamine, 10% (v/v) fetal bovine serum, and 1% (w/v) penicillin/streptomycin). Cells were incubated for 44 h at 37 ± 1 °C, followed by the addition of 6 µg/mL of cytochalasin B (Sigma, St. Louis, MO, catalog number: C6762). Vials were incubated for another 28 hours, then cultures were transferred to Falcon tubes and centrifuged at 800 rpm for 5 min. Then, the supernatant was removed, and the cell pellet was lightly shaken and centrifuged again after the addition of 5 mL of a fixative (5:1 methanol:acetic acid) and 3 drops of formaldehyde to the tubes. This procedure was repeated twice, using a 3:1 fixative and without formaldehyde. Finally, the supernatant was discarded, and 2–4 drops of the cell suspension were dripped onto slides, which were stained with a 5% Giemsa (Sigma, St. Louis, MO, catalog number: 48900) solution for 7 min. The previously coded slides were analyzed in a blinded test with the aid of an optical microscope (1000×), and the cytogenetic damage present in 1000 cells per slide was counted in duplicate.

Alkaline comet assay

The alkaline version of the comet assay was conducted according to the procedure described by Speit and Rothfuss (2012) and modified by de Lima et al. (2020). Briefly, 10 µL aliquots of S-180 (0.5×10^6 cells/mL) and HL-60 (0.8×10^6 cells/mL) cell suspensions were mixed with a thin layer of 0.75% low melting point agarose (90 µL) and placed on pre-coated slides with 1.5% normal melting point agarose (Sigma, St. Louis, MO, catalog numbers: A9539). Slides were dipped in a lysis solution (2.5 M NaCl, 100 mM EDTA, and 10 mM Tris, pH 10, with the addition of 1%

Triton X-100 and 10% DMSO (Sigma, St. Louis, MO, catalog numbers: S9888, ED, X100 and 276855, respectively) at the time of use) for up to 72 h at 4 °C, incubated in alkaline buffer (300 mM NaOH and 1 mM EDTA, pH >13) for 20 min, and then exposed to an electric current of 300 mA and 25 V (0.90 V/cm) for 15 min in an electrophoretic cell. At the end, slides were neutralized with Tris buffer (0.4 M and pH 7.5) and stained with a silver solution. Slides were then analyzed for the photomicrograph profile of the cells (at a magnification of 400× under an optical microscope), and the results were expressed as damage index (ID) and frequency of damage (FD) for 100 cells in duplicate. ID was calculated using the following formula: ID = Σ (number of cells in a given damage class x harm class), ranging from 0 to 400, while FD was calculated by the following formula: FD = 100–number of class 0 cells.

Hydrogen peroxide (H_2O_2)-induced genotoxicity test

This test was done according to the method described by Luz et al. (2013) and modified by de Lima et al. (2020). Briefly, 10 µL aliquots of S-180 cell suspension (0.5×10^6 cells/mL) were mixed with a thin layer of 0.75% low melting point agarose (90 µL) and placed on pre-coated slides with 1.5% normal melting point agarose. Slides were then exposed to Pyt (14.16 µM) and/or H_2O_2 (10 mM/mL) for 5 min. Slides were then dipped in a lysis solution (2.5 M NaCl, 100 mM EDTA, and 10 mM Tris (pH 10.0), with the addition of 1% Triton X-100 and 10% DMSO at the time of use) for 5 min at 4 °C. After this procedure, the comet assay was continued as discussed above.

Statistical analysis

Results are expressed as the mean ± standard deviation (SD). All determinations were conducted in duplicate, and the data were subjected to a two-way analysis of variance (ANOVA). Statistical analysis was performed using the Tukey's test for significance with the aid of the GraphPad Prism program (San Diego, CA, USA) by considering $p < 0.05$ at 95% confidence intervals.

Results

Cell viability assay

The effects of Pyt and controls on S-180 and HL-60 cell lines are presented in Fig. 1. The findings exhibited that both Pyt and Dox exert significant cytotoxic effects on the cell lines after 72 h of exposure. It produced more prominent effects against HL-60 cell lines as compared to S-180, and the overall effects were comparable to those of a standard drug. Half-minimal inhibitory concentrations (IC_{50}s) for S-180 and HL-60 cell lines were 18.98 ± 3.79 and 1.17 ± 0.34 µM, respectively.

Genotoxic effects on S-180 cells

Pyt exerted significant genotoxic effects at all tested concentrations. The overall effect was concentration-dependent with maximum damage at 14.16 µM on the S-180 cell line (Fig. 2). It was also observed that it significantly increased the index and frequency of damage as compared to untreated tumor cells.

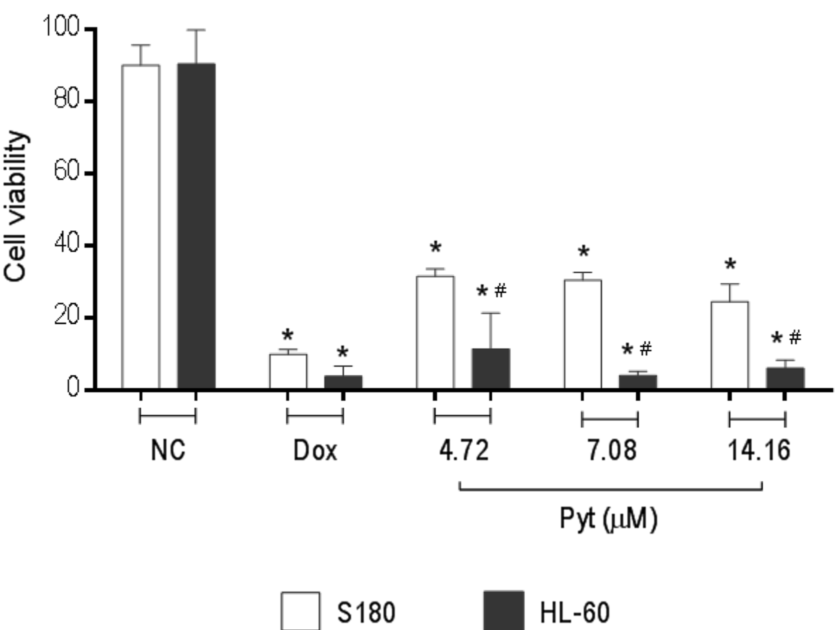


Fig. 1 Cell viability assessed by the trypan blue exclusion test in S-180 and MTT assay in HL-60 after 72 h of exposure. Values are mean ± SD, four independent experiments; ANOVA, two-way, followed by Tukey post-test at *$p < 0.05$ compared to the NC group; #$p < 0.05$ compared to S180 group, at the same concentration; NC: untreated cells; Dox: Doxorubicin (6 µM); Pyt: Phytol

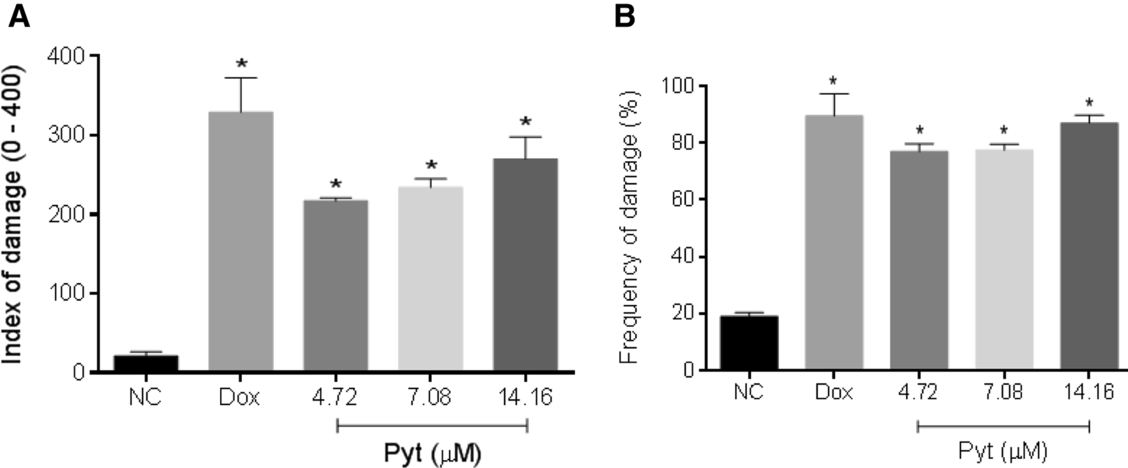


Fig. 2 Genotoxicity of phytol and doxorubicin in S-180 after 72 h of exposure. Values are mean ± SD, four independent experiments; ANOVA, two-way, followed by Tukey post-test at *p <0.05 compared to the NC group; (A) Damage index; (B) Frequency of damage; NC: Untreated cells; Dox: Doxorubicin 2 μg; Pyt: Phytol

The photomicrographs show the differences between the study groups in relation to the types (classes) of DNA damage (0, 1, 2, 3, and 4). The Pyt showed similarity of damage with the Dox-treated group, especially at 7.08 and 14.16 μM, by the frequency of types 3 and 4, indicative of apoptosis, as presented in Fig. 3.

(A) Cells without treatment; (B) Cells treated with doxorubicin 6 μM; (C and D) Cells treated with phytol 4.72 and 7.08 μM; (E and F) Cells treated with phytol 14.16 μM; T0-T4: Type 0 to type 4 damages; Ap: Apoptosis.

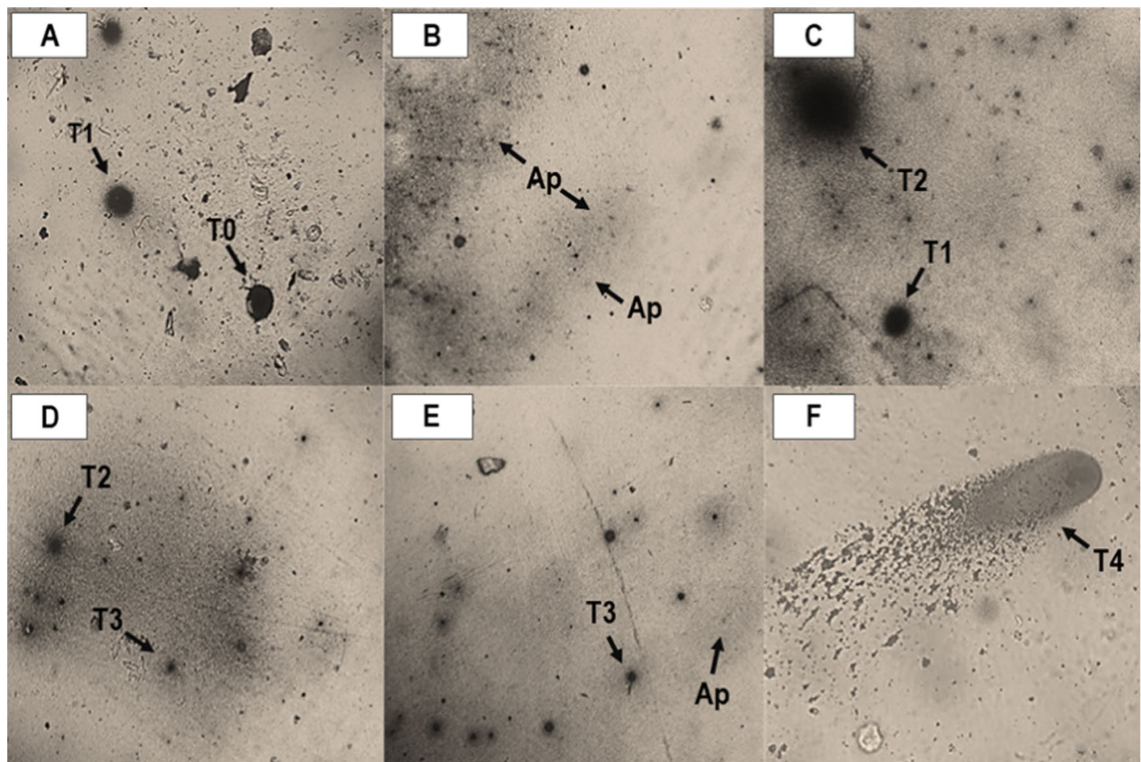


Fig. 3 Photomicrographic profile of S-180

Oxidative damage induced in S-180 cells

The effect of oxidative damage induced by Pyt in S-180 is presented in Table 1. It caused significant genotoxicity when S-180 cells were treated with Pyt with H_2O_2.

Cytogenetic effects in S-180 and HL-60 cells

Pyt at 14.16 μM increased the formation of micronuclei and showed a mutagenic effect on S-180 and HL-60 cells. It also significantly ($p < 0.05$) increased the number of nuclear bridges and shoots in a concentration-dependent manner when compared to the negative control (NC) group. The cytotoxic effects of Pyt were also observed by means of the cell division index (IDN) in a concentration-dependent fashion, as indicated by the rates of apoptosis and necrosis (Table 2 and 3, and Figs. 4 and 5).

Figure 4 shows the cytogenetic markers for the cytotoxic and antitumor effects of Pyt, such as the MN, nuclear bridges and buds, triadradial figures (trilobular nucleus), binucleate cells, apoptosis, and necrosis.

Arrows point to: (A) Necrosis, (B) Necrosis co-occurring with a triradial figure, (C) Isolated triradial figure, (D) Micronucleus, (E) Apoptotic cell, (F) Nucleoplasmic bridge.

Table 1 Oxidative stress-induced genotoxic effects of phytol and/or controls in S-180 co-treated with H_2O_2

Parameters	Groups			
	NC	H_2O_2	Pyt	Pyt + H_2O_2
ID (0 - 400)	40.7 ± 7.80	178.0 ± 2.44*	166.3 ± 23.34*	164.3 ± 18.52*
FD (%)	61.5 ± 5.91	97.7 ± 0.95*	95.5 ± 2.63*	96.7 ± 1.89*

Values are mean ± SD of four independent experiments. NC: Untreated cells. H_2O_2: Hydrogen peroxide (10 mM). Pyt: Phytol (14.16 μM). ANOVA, one-way, followed by Tukey post-test. *$p < 0.05$ compared to the CN group

Table 2 Cytogenetic damage profiles in phytol and control groups in S-180 after 72 h of exposure (CBMN test)

Treatments	Cytogenetic damages			Cytotoxicity	
S180					
	MN	Bridges	Buds	IDN	IDNC
NC	1.75 ± 1.02	2.80 ± 0.41	1.70 ± 0.12	1.69 ± 0.037	1.60 ± 0.033
Dox	36.50 ± 0.35[a]	35.5 ± 3.53[a]	17.0 ± 1.41[a]	1.11 ± 0.04[a]	1.23 ± 0.007[a]
Pyt 4.72 μM	8.00 ± 0.70	5.55 ± 2.12	2.00 ± 1.41	1.40 ± 0.018	1.26 ± 0.062
Pyt 7.08 μM	10.70± 1.76	8.50 ± 2.25[a]	11.0 ± 1.82[a]	1.35 ± 0.281	1.19 ± 0.146[a]
Pyt 14.16 μM	29.70 ± 3.18[a]	27.00 ± 7.04[abc]	28.50 ± 2.12[a]	1.25 ± 0.054[a]	1.16 ± 0.032[a]

Values are mean ± SD of four independent experiments. NC: Untreated cells. Dox: Doxorubicin 2 μg. Pyt: Phytol. MN: Micronucleus. IDN: Nuclear division index. IDNC: Nuclear division index considering apoptosis and necrosis. ANOVA, one-way, followed by Tukey post-test. [a]$p < 0.05$ compared to the NC, [b]$p < 0.05$ compared to the Pyt 4.72. [c]$p < 0.05$ compared to the Pyt 7.08

Table 3 Cytogenetic damage caused by phytol and control groups in HL-60 after 72 h of exposure (CBMN test)

Treatments	Cytogenetic damages			Cytotoxicity	
HL-60					
	MN	Bridges	Buds	IDN	IDNC
NC	2.00 ± 1.41	2.50 ± 0.70	1.50 ± 0.70	1.73 ± 0.03	1.64 ± 0.004
Dox	28.0 ± 11.3[a]	41.5 ± 7.77[a]	26.00 ± 2.80[a]	1.07 ± 0.002[a]	1.16 ± 0.007[a]
Pyt 4.72 μM	9.50 ± 3.53	13.0 ± 1.41	11.00 ± 2.42	1.55 ± 0.12	1.36 ± 0.14
Pyt 7.08 μM	12.50 ± 3.45[a]	19.5 ± 2.21	25.00 ± 4.23	1.30 ± 0.08	1.24 ± 0.07[a]
Pyt 14.16 μM	26.00 ± 5.65[a]	39.0 ± 5.65[a]	28.50 ± 2.12[a]	1.33 ± 0.12	1.24 ± 0.05[a]

Values are mean ± SD of four independent experiments. NC: Untreated cells. Dox: Doxorubicin 2 μg. Pyt: Phytol. MN: Micronucleus. IDN: Nuclear division index. IDNC: Nuclear division index considering apoptosis and necrosis. ANOVA, one-way, followed by Tukey post-test. [a]$p < 0.05$ compared to the NC group

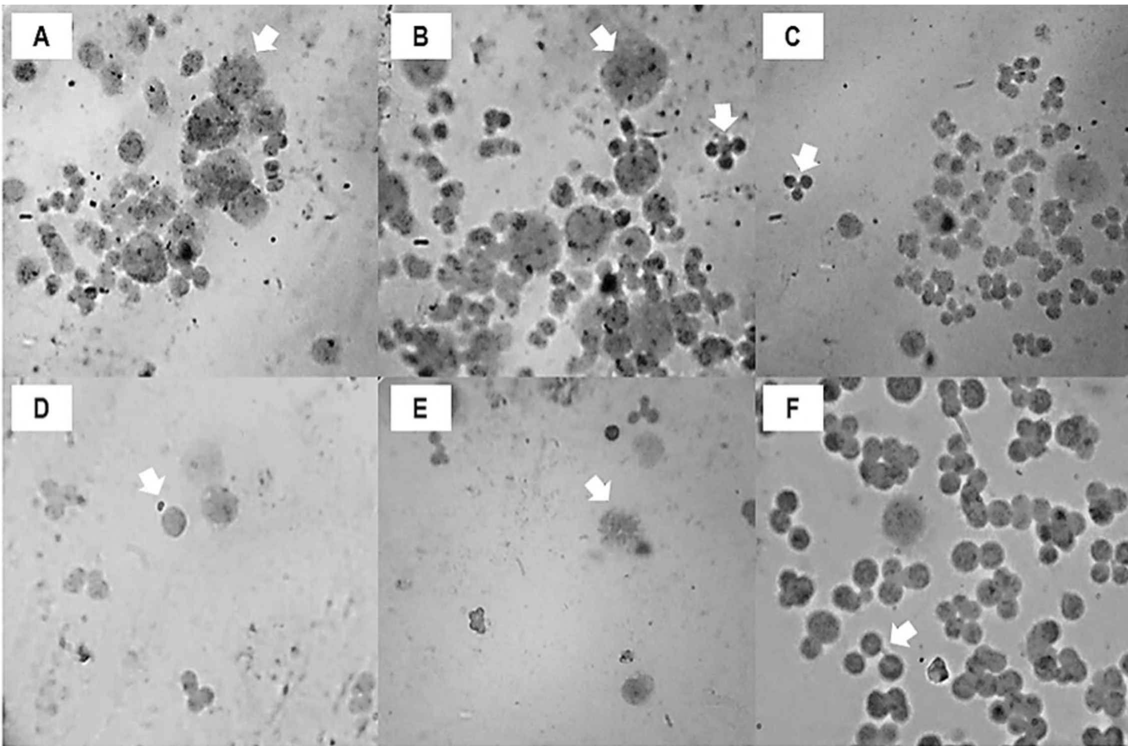


Fig. 4 Photomicrographic profile of HL-60 treated with phytol 14.16 μM in the CBMN test

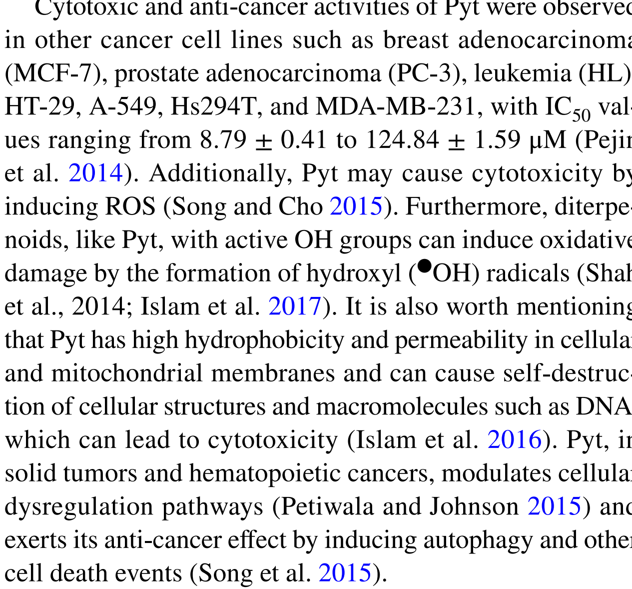
Apoptosis and necrosis effects in S-180 and HL-60 cells

As shown in tables 2 and 3 and in Figs. 6 A and B, the results of our study pertaining to apoptosis and necrosis caused by Pyt in S-180 and HL-60 cells were evaluated by the CBMN test. Our findings reveal that Pyt at all tested concentrations significantly increased the number of apoptosis (Fig. 6 A) and necrosis (Fig. 6 B) at 14.16 μM compared to the NC group, indicating a cytotoxic action on S-180 cells; similar results were also observed in the HL-60 cell line. It should be noted that differences were observed between the effects of Pyt and the standard anti-neoplastic drug Dox (Fig. 6 A and B).

Discussion

Natural products and their derivatives have historically been a valuable source of therapeutic agents (Dey et al. 2016). In this context, terpenoids are cytotoxic to tumor cells and thus can be used as chemotherapeutic or chemo-preventive agents and as adjuvants in cancer therapies (Ghosh 2012). Our findings in this study show that Pyt can induce cytotoxicity in S-180 and HL-60 cell lines by inhibiting cell viability in the blue trypan and MTT assays. Cytotoxic drugs may inhibit cell viability through mechanisms associated with cell cycle trimming and the induction of apoptosis (Tajudin et al. 2012).

Cytotoxic and anti-cancer activities of Pyt were observed in other cancer cell lines such as breast adenocarcinoma (MCF-7), prostate adenocarcinoma (PC-3), leukemia (HL), HT-29, A-549, Hs294T, and MDA-MB-231, with IC_{50} values ranging from 8.79 ± 0.41 to 124.84 ± 1.59 μM (Pejin et al. 2014). Additionally, Pyt may cause cytotoxicity by inducing ROS (Song and Cho 2015). Furthermore, diterpenoids, like Pyt, with active OH groups can induce oxidative damage by the formation of hydroxyl ($^{\bullet}$OH) radicals (Shah et al., 2014; Islam et al. 2017). It is also worth mentioning that Pyt has high hydrophobicity and permeability in cellular and mitochondrial membranes and can cause self-destruction of cellular structures and macromolecules such as DNA, which can lead to cytotoxicity (Islam et al. 2016). Pyt, in solid tumors and hematopoietic cancers, modulates cellular dysregulation pathways (Petiwala and Johnson 2015) and exerts its anti-cancer effect by inducing autophagy and other cell death events (Song et al. 2015).



Published research showed that Pyt exhibited concentration-dependent cytotoxic activity in MCF-7 and PC-3 cell lines, which may suggest its usage for the manufacture of anti-cancer drugs (NCI 2014). In a recent study, it exerted anti-cancer effects on RAW264.7 cells via suppressing osteoclast differentiation and oxidative stress through the nuclear factor erythroid 2–related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway (Kim et al. 2022). In addition, due to its cytotoxicity, it can also be a candidate for the design of new

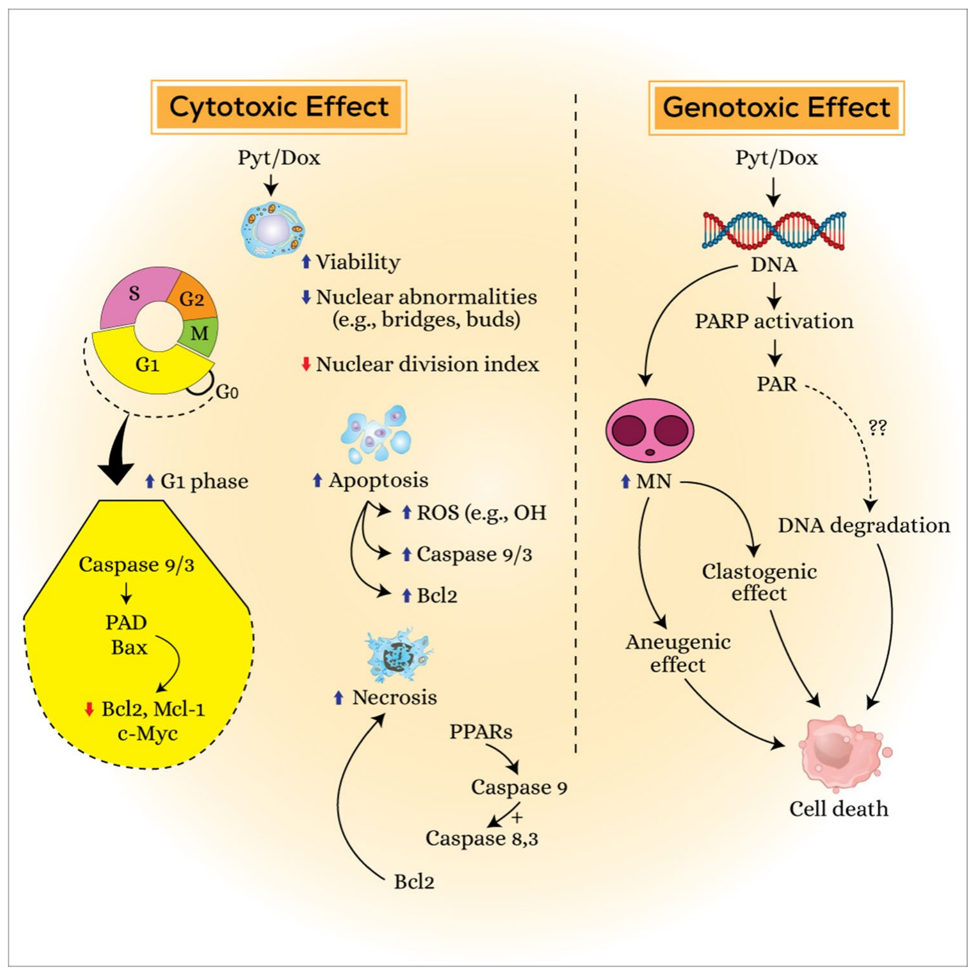
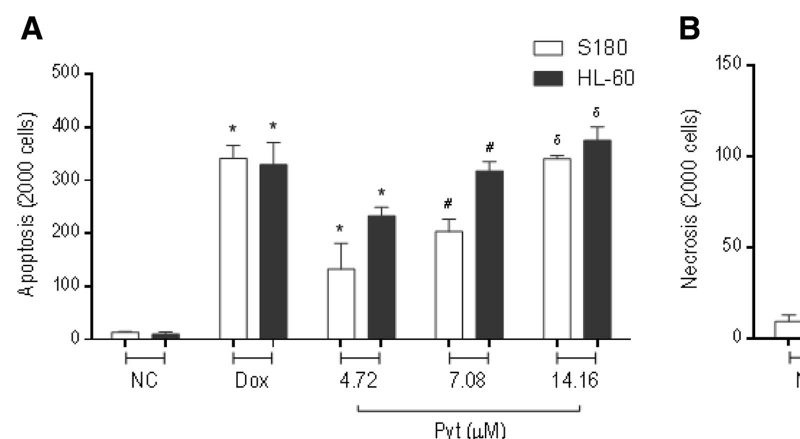


Fig. 5 Possible cytogenotoxic effect mechanism of phytol in the test systems



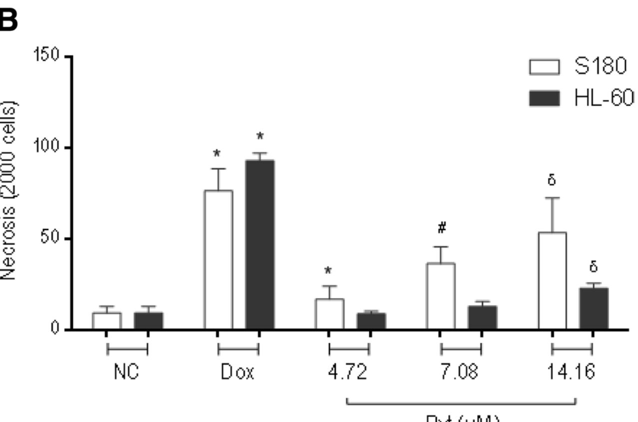


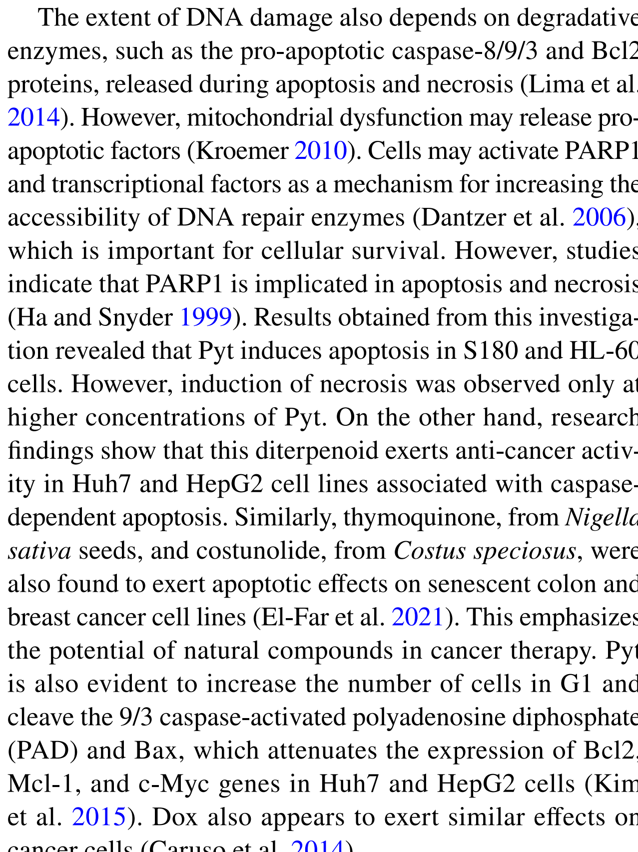
Fig. 6 Apoptosis and necrosis induced by phytol in S-180 and HL-60 cell lines after 72 h of exposure. [(A) Apoptosis; (B) Necrosis; Values are mean ± SD, four independent experiments; ANOVA, two-way, followed by Tukey post-test. *p <0.05 compared to the NC; #p <0.05 compared to the NC and Pyt 4.72; δp <0.05 compared to the NC and Pyt 4.72 and Pyt 7.08 μM; NC: Untreated cells; Dox: Doxorubicin 6 μM; Pyt: Phytol]

drugs, considering the selectivity of this diterpenoid (Pejin et al. 2014). On the other hand, genetic toxicity analysis can be performed by means of the *in vitro* and *ex vivo* comet assay for assessment of DNA damage and DNA repair capability (Pourrut et al. 2015), and in its alkaline version, it can detect SSBs and/or DSBs, alkali-labile sites, and oxidative

damage (Davison 2016). In genotoxicity analysis, Pyt, at all concentrations, induced an increase in the ID and FD in S-180. It caused similar genotoxicity in S-180 as compared to H_2O_2, as it could generate $^{\bullet}OH$ (Islam et al. 2016). Pyt can also increase the levels of thiobarbituric acid substances (TBARS), cause lipid peroxidation, and cause a decrease in glutathione (GSH) enzymes (Leipnitz et al. 2010).

In HepG2 cells and using the luciferase activity assay, results from this study showed that Pyt directly activates peroxisome proliferator-activated receptors (PPARs) and indirectly through its phytaneic acid metabolite (FA) (Goto et al. 2005). FA inhibits histone deacetylase (Hdac2) and induces cell death, with cytotoxic effects associated with caspase-9, as observed in neuronal cells (Nagai 2015), as well as generate free radicals during β-oxidation (Tamatani et al. 1999), causing oxidative stress with potential DNA damage (Stadelmann-Ingrand et al. 2004). On the other hand, depolymerase inhibitors (ADP-ribose)-polymerase (PARP), such as it, cause DNA damage and may inhibit repair pathways such as base excision repair (BER), and therefore are considered promising as antineoplastic drugs (Velic et al. 2015).

Genotoxic damage with higher intensity triggers unrepaired genomic instability coupled with extensive genotoxicity, which at the chromosomal/molecular level can cause mutations in DNA (Zhang et al. 2014). This may be due to the ability of chromosomal damage, rearrangement, nondisjunction, gene amplification, necrosis, and apoptosis to result in the formation of MN (mainly from chromosomal fragments or whole chromosomes that fail to be directed to the mitotic spindle when the cell divides) (Bhatia and Kumar 2013). Chromosomal instability contributes to human neoplasms through chromosome malsegregation, aneuploidy, damage to DNA, mutations, and chromosome translocations. An earlier study indicated that these chromosomal alterations may contribute to the formation of MN, which may be important for cancer therapy (Bakhoum and Compton 2012). In this study, Pyt induced mutagenicity by initiating nuclear MN bridges and buds in S-180 and HL-60 cells, especially at the highest concentrations tested, leading to cytotoxicity determined by IDN. The increase in MN frequency is associated with deficiencies in DNA damage responses. MN represents fragmentation and/or loss of whole chromosomes (Maluf and Erdtmann 2001). In addition, they are markers to detect clastogenic and aneugenic agents in genotoxic and mutagenic compounds (Kirsch-Volders et al. 2011). Nucleoplasmic bridges are derived from chromosomal rearrangements and fusion of telomeres (Fenech 2000), and the nuclear buds represent DNA amplification, in which telomerase has an important role in this cytogenetic alteration (Fenech et al. 2011). Manifestations of gene amplification are associated with malignant phenotypes and may arise during the cell cycle from extra-chromosomal material (Shimizu 2009).



The extent of DNA damage also depends on degradative enzymes, such as the pro-apoptotic caspase-8/9/3 and Bcl2 proteins, released during apoptosis and necrosis (Lima et al. 2014). However, mitochondrial dysfunction may release pro-apoptotic factors (Kroemer 2010). Cells may activate PARP1 and transcriptional factors as a mechanism for increasing the accessibility of DNA repair enzymes (Dantzer et al. 2006), which is important for cellular survival. However, studies indicate that PARP1 is implicated in apoptosis and necrosis (Ha and Snyder 1999). Results obtained from this investigation revealed that Pyt induces apoptosis in S180 and HL-60 cells. However, induction of necrosis was observed only at higher concentrations of Pyt. On the other hand, research findings show that this diterpenoid exerts anti-cancer activity in Huh7 and HepG2 cell lines associated with caspase-dependent apoptosis. Similarly, thymoquinone, from *Nigella sativa* seeds, and costunolide, from *Costus speciosus*, were also found to exert apoptotic effects on senescent colon and breast cancer cell lines (El-Far et al. 2021). This emphasizes the potential of natural compounds in cancer therapy. Pyt is also evident to increase the number of cells in G1 and cleave the 9/3 caspase-activated polyadenosine diphosphate (PAD) and Bax, which attenuates the expression of Bcl2, Mcl-1, and c-Myc genes in Huh7 and HepG2 cells (Kim et al. 2015). Dox also appears to exert similar effects on cancer cells (Caruso et al. 2014).

Polyphenols, especially tannins and flavonoids, may have chemo-preventive and anti-tumor properties (Zhao et al. 2015). This is further supported by studies indicating the anticancer potential of other compounds like the antimetabolite pemetrexed and the herbal polyphenol honokiol, which, when co-delivered using a novel self-assembled nanogel comprising natural polysaccharides and functional proteins, showed superior *in vitro* cytotoxicity (Atallah et al. 2022). Studies indicated the anti-cancer potential of terpenoids isolated from spleen oils in MCF-7 cells (wild-type p53) and MDA-MB-231 cells by inhibiting cell viability and proliferation and by inducing apoptosis with less cytotoxic effects in non-tumor cells. In both cell lines, apoptosis can be induced by activation of caspase-8/9 and cleavage of the PARP protein (Santha et al. 2013). In this context, Pyt induces apoptosis in AGS gastric adenocarcinoma cells, as indicated by the increase of cells in the sub-G1 mitotic phase, low Bcl-2 regulation, Bax overexpression, 9/3 caspase activation, PARP cleavage, mitochondrial membrane depolarization, induction of autophagy and cytotoxicity by the generation of ROS, and decreased expression of the p62 gene (Song and Cho 2015). Pyt also inhibits MB-231 tumor cells in a concentration-dependent manner, especially at 1 μM, and induces autophagy by increasing organelles with acidic enzymes (Song et al. 2015).

It should be emphasized that necrosis is also modulated by PARP1 *via the* induction of DNA damage. Some studies

suggest that this protein mediates cell death (Bredholt et al. 2015). These mechanisms are also reported for Dox, including increased mitochondrial respiration, induction of DNA damage *via* ROS, generation of nitric oxide with a decrease in PARP1, and changes in the cell cycle. However, Dox did not inhibit p53, suggesting that the anti-neoplastic-induced PARP1-dependent necrosis was independent of the *TP53* gene (Shin et al. 2015).

Conclusions

Pyt, especially at the two highest concentrations (7.08 and 14.16 µM), induced cytotoxic as well as anti-cancer effects in S-180 and HL-60 cell lines similar to those of Dox. The anticancer effect of Pyt was observed by the following different cytogenetic mechanisms: (1) induction of cytotoxicity by reduction of cell viability, interference with the free nuclear division index, and consideration of apoptosis and necrosis (2) induction of genotoxicity, possibly *via* induction of oxidative stress (3) clastogenic and/or aneugenic effects by induction of MN (4) nuclear abnormalities indicating cytotoxicity by increasing the nuclear bridges and buds; and (6) induction of apoptosis and necrosis. Pyt may be an important alternative chemotherapeutic agent.

Authors contributions MVOB, MTI – Data collection and primary drafting; AMOFM, ACR, RMTL, JROF – Data collection; JMCS, PMPF, AACMC – Study design, project supervision; AR, HAH, KFA, HK – Editing and final drafting.

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Data availability Not appilcable

Declarations

Conflicts of interest None declared.

Ethical approval Not applicable

Consent to participate Not applicable

Consent to publish Not applicable

Competing interests The authors declared no competing interest.

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PRÓPOLIS VERMELHA E AÇÃO ANTIFÚNGICA: POTENCIALIDADES E DESAFIOS

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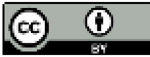

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RESUMO: Introdução: a própolis é uma composição resinosa produzida por abelhas e utilizada em suas colmeias contra microrganismos. Existem diversos tipos desse composto, sendo o de coloração vermelha o último espécime relatado na literatura. Assim, dentre suas aplicabilidades, a atividade antifúngica da própolis vermelha tem sido explorada com vistas a ampliar sua ação terapêutica. Objetivo: explorar estudos acerca da ação antifúngica da própolis vermelha, identificando suas potencialidades e desafios. Metodologia: foi realizada uma revisão integrativa nas bases de dados bibliográficos MEDLINE (via PubMed), SciELO e Google Acadêmico, complementada por uma diligência nas bases de ensaios clínicos ReBEC e Clinical Trials. Em seguida todos os estudos selecionados foram explorados para obtenção do cenário atual sobre o tema. Resultados: foram incluídos 08 estudos, sendo 01 deles um ensaio clínico. Os estudos comprovam a ação antifúngica da própolis vermelha, principalmente contra Candida spp. e Paracoccidioides brasiliensis, e evidenciam a maior potência fungicida deste composto em detrimento de outros tipos de própolis. Conclusão: a ação antifúngica da própolis vermelha mostra-se uma potencialidade em diversos estudos. Entretanto, o volume de pesquisas científicas relativas a esse tema é insuficiente e a complexidade desse composto configura-se como um desafio à sua aplicabilidade.
PALAVRAS-CHAVE: Própolis Vermelha; Antimicrobiano; Antifúngico.

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RED PRÓPOLIS AND ANTIFUNGAL ACTIVITY: POTENTIALITIES AND CHALLENGES

ABSTRACT: Introduction: propolis is a resinous composition produced by compounds and used in their hives against microorganisms. There are several types of this compound, the red one is the last specimen reported in the literature. Thus, among its applicability, the antifungal activity of red propolis has been explored as a path to expand its therapeutic action. Objective: to explore studies about the antifungal action of red propolis, identifying its potentialities and challenges. Methodology: Na integrative review was carried out in the bibliographic databases MEDLINE (via PubMed), SciELO and Google Scholar, complemented by a diligence in ReBEC and Clinical Trials databases. Then, all selected studies were explorers to obtain the current scenario on the subject. Results: 08 studies were included, which 01 of them was a clinical trial. Studies prove the antifungal action of red propolis, mainly against Candida spp. and Paracoccidioides brasiliensis, and show the greater fungicidal power of this compound compared to other types of propolis. Conclusion: the antifungal action of red propolis shows potential in several studies. However, the volume of scientific research on this theme is insufficient and the complexity of this compound represents a challenge to its applicability.
KEYWORDS: Red Propolis; Antimicrobial; Antifungal.

PROPÓLEO ROJO Y ACCIÓN ANTIFÚNGICA: POTENCIALIDADES Y DESAFÍOS

RESUMEN: Introducción: el propóleo es una composición resinosa producida por las abejas y utilizada en sus colmenas contra los microorganismos. Existen varios tipos de este compuesto, siendo el rojo el último ejemplar reportado en la literatura. Así, entre sus posibilidades de aplicación, se ha explorado la actividad antifúngica del propóleo rojo con vistas a ampliar su acción terapéutica. Objetivo: explorar estudios sobre la acción antifúngica del propóleo rojo, identificando sus potencialidades y desafíos. Metodología: Se realizó una revisión en las bases de datos bibliográficas MEDLINE (vía PubMed), SciELO y Google Scholar, complementada con una diligencia en las bases de datos de ensayos clínicos ReBEC y Clinical Trials. Luego se exploraron todos los estudios seleccionados para obtener el escenario actual sobre el tema. Resultados: Se incluyeron 08 estudios, 01 de los cuales fue un ensayo clínico. Los estudios demuestran la acción antifúngica del propóleo rojo, principalmente contra Candida spp. y Paracoccidioides brasiliensis, y muestran el mayor poder fungicida de este compuesto en detrimento de otros tipos de propóleos. Conclusión: la acción antifúngica del propóleo rojo muestra potencial en varios estudios. Sin embargo, el volumen de investigación científica sobre este tema es insuficiente y la complejidad de este compuesto representa un desafío para su aplicabilidad.
PALABRAS CLAVE: Propóleo Rojo; antimicrobiano; Antifúngico.

1. INTRODUÇÃO

A própolis é uma composição resinosa preparada por abelhas, que a utilizam na estruturação física das colmeias e na proteção do alveário contra microrganismos e insetos (RADCLIFFE, 2021). Em relação à sua matéria-prima, a própolis é constituída

por secreções salivares de abelhas, pólen, óleos essenciais, madeira, fragmentos de terra, resinas vegetais e exsudados vegetais encontrados em caules, folhas e flores (SANTOS *et al.*, 2020; HERRERA-LÓPEZ *et al.*, 2023). Por esse motivo, tipos variados desse composto podem ser encontrados na natureza, de forma que o mais recente espécime descoberto e reportado na literatura foi o de coloração vermelha (ALENCAR *et al.*, 2007), o que justifica a necessidade de elevar a compreensão sobre seus efeitos.

A própolis vermelha tem muitos de seus componentes provenientes da espécie vegetal *Dalbergia ecastophyllum*, a qual é apontada como uma de suas principais fontes (MOISE e BOBIŞ, 2020). No Brasil, essa planta pode ser encontrada na região nordeste do país, principalmente em áreas litorâneas (SILVA *et al.*, 2022). Além do Brasil, essa variedade de própolis foi reportada em outros países, a saber: Cuba, México, China e Venezuela (SANTOS *et al.*, 2020); o que denota interesse transnacional sobre o tema.

Assim, devido à sua complexa composição química, a própolis vermelha detém diferentes ações biológicas, a exemplo da atividade antiviral (VARIANI *et al.*, 2017; SILVA-BELTRÁN *et al.*, 2022) e antimicrobiana (VALVERDE *et al.*, 2023). Destas, a atividade antimicrobiana da própolis vermelha tem sido alvo de inúmeros estudos, os quais abarcam desde sua ação antibacteriana (OLIVEIRA NETO *et al.*, 2022), até sua potencialidade antifúngica (SANTOS *et al.*, 2021; SIQUEIRA *et al.*, 2009) que, em especial, representa uma nova possibilidade terapêutica e de assepsia. Nesse sentido, muitos compostos com atividade antifúngica foram encontrados na própolis vermelha (MENDONÇA *et al.*, 2015), tal qual flavonoides – como a formononetina (NEVES *et al.*, 2016) – e outros que podem interferir nos processos biológicos dos microrganismos fúngicos, a exemplo da síntese de ergosterol (PIPPI *et al.*, 2015), encontrada na membrana celular destes seres.

Frente ao exposto, é imprescindível que a ação antifúngica da própolis vermelha seja objeto de novos estudos. Por esse motivo, o objetivo do presente trabalho é reunir dados bibliográfico e ensaios clínicos recentes, com vistas à compreensão teórica e prática das potencialidades e dos desafios relativos à atividade antifúngica da própolis vermelha, de maneira a ampliar seu horizonte terapêutico

2. MATERIAIS E MÉTODO

Para alcançar um panorama sobre o tema proposto, foi empreendida uma busca a partir das bases de dados bibliográficos MEDLINE (via *PubMed*), *SciELO* e Google Acadêmico, complementada por uma diligência nas bases de ensaios clínicos ReBEC

(Registro Brasileiro de Ensaios Clínicos) e *Clinical Trials* (Sistema de registro de estudos clínicos norte-americano).

2.1 Bases de dados bibliográficos

Para uma busca sistematizada nas bases de dados bibliográficos, foram utilizados os termos "*red*", "*propolis*" e "*antimicrobial*" com o operador booleano "*AND*" entre as três palavras. É importante enfatizar que os termos "*red*" e "*propolis*" foram adicionados separadamente para permitir a obtenção de uma maior quantidade de estudos, uma vez que alguns artigos usam a locução "*red propolis*" enquanto outros possuem algum termo entre estas palavras, que também podem aparecer invertidas. Em relação ao termo "*antimicrobial*", este foi selecionado em detrimento da expressão "*antifungal*", pois com esta havia menor quantidade de trabalhos existentes, conforme evidenciado por testes de descritores realizados antes do início deste estudo.

Em seguida, os trabalhos obtidos foram submetidos aos seguintes critérios de inclusão: I - Estudos empíricos; II - Período de publicação de 2018 a 2023; III - Idiomas português, espanhol ou inglês. Além disso, foram aplicados os seguintes critérios de exclusão: I - Artigos que não exploravam a ação antifúngica da própolis vermelha; II - Revisões bibliográficas; III - Teses; IV - Dissertações; V - Resumos. Assim, os estudos obtidos após tais etapas foram incluídos nesta obra.

Destarte, a busca realizada na base *PubMed* retornou 55 artigos, que então foram submetidos aos critérios de inclusão e exclusão, remanescendo 4 artigos. Na base de dados bibliográficos *SciELO*, a busca inicial retornou 6 artigos, de forma que restaram apenas 2 após a aplicação dos critérios de inclusão e de exclusão. Por último, a busca na base Google Acadêmico retornou 36 estudos, dentre os quais somente 3 atendiam os critérios de inclusão e de exclusão.

Com vistas à unificação das buscas, os artigos encontrados em mais de uma base de dados foram comparados para assegurar a ausência de duplicidade, de modo que foram incluídos 7 estudos como resultado da presente metodologia, conforme ilustra o fluxograma presente na Figura 1.

Figura 1: Fluxograma de buscas.
Fonte: Elaborado pelos autores (2023).

2.2 Bases de ensaios clínicos

Com vistas à obtenção do maior número de estudos elegíveis, a busca na base de ensaios clínicos ReBEC foi promovida apenas com a palavra "propolis", para que em seguida os ensaios encontrados fossem avaliados segundo os mesmos critérios de inclusão e exclusão supracitados, exceto a restrição a estudos realizados antes de 2018. Assim, a busca retornou 20 ensaios clínicos, dos quais todos foram excluídos após leitura completa, uma vez que não dizem respeito à ação antifúngica da própolis vermelha. Na base de ensaios clínicos *Clinical Trials*, a busca pelo termo "propolis" retornou 98 ensaios clínicos, dos quais 97 foram excluídos após leitura completa por não abordarem a ação antifúngica da própolis vermelha, restando apenas um ensaio clínico a ser incluído no presente trabalho.

3. RESULTADOS

3.1 Perfil Antifúngico

A partir das bases de dados bibliográficos MEDLINE (via *PubMed*), *SciELO* e Google Acadêmico, foram obtidos sete estudos acerca da ação antifúngica da própolis vermelha. Estes estudos estão representados na Tabela 1, que ilustra os valores relativos ao diâmetro da área de inibição fúngica promovido pela ação da própolis vermelha, assim como sua Concentração Inibitória Mínima (CIM) e Concentração Fungicida Mínima (CFM) em relação a diferentes espécies e cepas de fungos.

Tabela 1: Estudos *in vitro* sobre a ação antifúngica da própolis vermelha

Publicação	Diâmetro da Área de Inibição	CIM e CFM	Espécie de fungo
Botteon *et al.* (2021)	O estudo não apresentou dados de diâmetro da área de inibição.	CIM de 0,00156 a 0,25000 mg/mL. CFM não informado.	*Candida albicans* (ATCC 28366)
Marroquim *et al.* (2018)	O estudo não apresentou dados de diâmetro da área de inibição.	O estudo não apresentou dados de CIM ou CFM.	*Candida albicans* (cepa não identificada)
Moreira *et al.* (2022)	O estudo não apresentou dados de diâmetro da área de inibição.	CIM de 0,032 a 0,128 mg/mL e CFM de 0,128 mg/mL	*Candida albicans* (ATCC 24433)
Sampaio *et al.* (2021)	O estudo não apresentou dados de diâmetro da área de inibição.	O estudo não apresentou dados de CIM ou CFM.	*Candida albicans* (ATCC 90028)
Santos *et al.* (2021)	O estudo não apresentou dados de diâmetro da área de inibição.	O estudo não apresentou dados de CIM ou CFM.	*Paracoccidioides brasiliensis* (Pb18)
Silva *et al.* (2019)	De 10,4mm a 12,4mm;	O estudo não apresentou dados de CIM ou CFM.	*Candida albicans* (ATCC 10231) e *Candida Krusei* (ATCC 6258).
Sokolonski *et al.* (2021)	O estudo não apresentou dados de diâmetro da área de inibição.	CIM de 0,015 a 4,000 mg/mL e CFM de 0,125 a 4,000 mg/mL.	Candida *albicans* (IOC 2508, IOC 2517, [...]), Candida *dubliniensis (*PAC 1), e Candida *tropicalis* (PAC2, PAC4, [...]).

Fonte: Elaborado pelos autores (2023).

Nesse sentido, no estudo de Botteon *et al.* (2021) foram produzidas nanopartículas de ouro com extrato de própolis vermelha que demonstraram propriedades biológicas significativas, dentre as quais o poder fungicida deste composto, alcançando uma concentração inibitória mínima entre 0,00156 e 0,25 mg/mL. Nessa mesma perspectiva, Moreira *et al.* (2022) obtiveram complexos de inclusão de β-ciclodextrina com própolis vermelha e avaliaram sua atividade antimicrobiana na cavidade oral, resultando em uma concentração inibitória mínima entre 0,032 e 0,128 mg/mL contra cepas de *Candida albicans*. Além disso, estes autores indicam que, ao associar nistatina ao complexo, houve um aumento na atividade antifúngica da própolis vermelha. Em outro estudo, Sampaio *et al.* (2021) utilizaram o extrato etanólico de própolis vermelha para modificar a cimentação de bandas ortodônticas e em seguida avaliar, dentre outras propriedades, sua atividade antimicrobiana. Frente a isso, descobriram que o cimento de ionômero de vidro contendo 25% de extrato etanólico de própolis vermelha mostrou um aumento significativo em sua atividade antifúngica contra *Candida albicans*, enquanto suas propriedades mecânicas e de liberação de flúor permaneceram sem alterações significativas. Efeito similar foi reportado por Marroquim *et al.* (2018), que investigaram a atividade antifúngica de capas metálicas ortodônticas feitas com cimento de fosfato de zinco contendo própolis vermelha em diferentes concentrações, dentre as

quais os autores afirmam que as concentrações de 5% e 3% promoveram efeito inibitório significativo.

Outrossim, os demais estudos averiguaram o efeito antifúngico da própolis vermelha *in vitro*. Desse modo, Silva *et al*. (2019) tiveram como objetivo avaliar a atividade antimicrobiana, antifúngica, antioxidante, antitumoral e a toxicidade do extrato etanólico de própolis vermelha, além da determinação de sua composição química, concluindo que esse extrato pode ser considerado uma fonte potencial de metabólitos bioativos ao alcançar diâmetros da área de inibição entre 10,4 e 12,4 milímetros em relação aos fungos testados, a depender de sua concentração. Nessa perspectiva, Santos *et al*. (2021) também investigaram o efeito antifúngico da própolis vermelha, aplicando-a em fungos causadores de paracoccidioidomicose e obtendo resultados que, além de indicarem o efeito antifúngico da própolis vermelha, apontam para sua ação na ativação de neutrófilos, na prevenção da disseminação fúngica e no controle do processo inflamatório excessivo. Vale lembrar que a paracoccidioidomicose é uma patologia fúngica que apresenta resistência a diversos antifúngicos conhecidos (VITIELLO *et al*., 2023).

Por fim, Sokolonski *et al*. (2021) realizaram uma comparação entre o efeito antifúngico da própolis vermelha e da própolis verde, aplicando-as em diferentes espécies de *Candida* spp. isoladas de lesões de estomatite protética e em cepas de referência. Assim, descobriram que a própolis vermelha pode ser encarada como um produto natural promissor para ser utilizado na terapia antifúngica auxiliar da estomatite protética. Além disso, concluíram que, mesmo nas menores doses testadas, o extrato da própolis vermelha apresentou maior atividade antifúngica quando comparado ao extrato da própolis verde.

3.2 Ensaios Clínicos

A partir do site de ensaios clínicos do governo dos Estados Unidos da América e do site Registro Brasileiro de Ensaios Clínicos (ReBEC), foi identificada a existência de apenas um ensaio clínico sobre o referido assunto, o qual está descrito na Tabela 2. Os resultados desse estudo foram publicados por Freires *et al*. (2016) e apontam como conclusão que o extrato de própolis vermelha apresenta forte atividade antifúngica contra *Candida* spp., uma vez que suas frações ativas foram capazes de romper as estruturas pré-formadas e maduras do biofilme fúngico, resultando em dano celular. Além disso, os autores concluem que a elevada presença de flavonoides na composição

química da própolis vermelha pode estar relacionada à promissora atividade antifúngica observada.

Tabela 2: Ensaio clínico sobre a ação antifúngica da própolis vermelha

Identificação	Status	Principais objetivos	Condição clínica	Intervenção
NCT02818803	Completo	Avaliar a eficácia e segurança da própolis no tratamento da candidíase oral.	Candidíase Oral e Estomatite Protética	Uso oral de extrato de própolis em gel 3x ao dia e comparado ao Miconazol.

Fonte: Elaborado pelos autores (2023).

4. DISCUSSÃO

É possível observar, frente a uma ampla análise dos estudos citados ao longo deste trabalho, que as evidências provenientes dos ensaios realizados ratificam a ação antifúngica da própolis vermelha. Entretanto, é importante salientar que apesar de a própolis ser um composto mundialmente conhecido há séculos, sua versão na cor vermelha foi descoberta recentemente, portanto são raros os estudos que dizem respeito à sua ação antifúngica – inviabilizando comparações fundamentais para determinar seu potencial antifúngico.

Nesse sentido, observam-se diferenças metodológicas entre os escassos estudos acerca do tema, o que dificulta esboçar correspondências entre os dados. Silva *et al.* (2019), por exemplo, utilizaram o método de disco difusão para promover a triagem da própolis vermelha em relação à sua ação antifúngica – de forma a encontrar valores de diâmetro da área de inibição –, enquanto Botteon *et al.* (2021), Sokolonski *et al.* (2021) e Moreira *et al.* (2022) empregaram a microdiluição como método. Não obstante, Marroquim *et al.* (2018), Sampaio *et al.* (2021) e Santos *et al.* (2021) não fizeram uso de ambos os métodos, impedindo uma comparação equalizada entre todos os estudos explorados neste trabalho. Outrossim, a maioria destes estudos avaliaram não apenas a ação antifúngica da própolis vermelha, mas também outros fatores, como sua atividade anticâncer (BOTTEON *et al.*, 2021), antibactericida (SILVA *et al.*, 2019; SAMPAIO *et al.*, 2020; MOREIRA *et al.*, 2022) e imunomodulatória (SANTOS *et al.*, 2021), o que impediu o aprofundamento acerca da ação antifúngica deste espécime de própolis em detrimento da investigação de outras atividades biológicas.

Em relação à espécie de fungo utilizada para ratificar a ação antifúngica da própolis vermelha, a maioria dos estudos optou pela *Candida albicans*, o que é importante para viabilizar novas formas de combate a esse microrganismo reconhecido

por sua alta resistência (KESSLER *et al*., 2022; GONG *et al*., 2023). À vista disso, os únicos autores que não investigaram sobre tal microrganismo foram Santos *et al.* (2021), que preferiram testar a atividade fungicida da própolis vermelha contra *Paracoccidioides brasiliensis.* Sobre este segundo fungo, sabe-se que possui elevada resistência (PITANGUI *et al.,* 2023*)* e, em especial, é encontrado no Brasil, onde tem emergido como uma ameaça (PEÇANHA *et al.,* 2022*)*, o que indica a importância de se estabelecer novos métodos terapêuticos que sejam mais eficientes contra esse microrganismo, a exemplo do uso da própolis vermelha, que poderia ser testada isolada ou em sinergia com outros antifúngicos conhecidos contra esse fungo (HAHN *et al.,* 2023*).*

Outro aspecto a ser considerado relaciona-se com o fato de a própolis vermelha ser uma composição heterogênea (SANTOS *et al*., 2020). Frente a isso, estudos acerca desse composto indicam que sua constituição é rica em xantonas, chalconas, auronas, catequinas e leucoantocianidinas (SILVA *et al*., 2019), além de elementos fenólicos, triterpenos, isoflavonóides, benzofenonas e naftoquinonas (MOREIRA *et al*., 2022). Por esse motivo, é esperado que amostras da própolis vermelha obtidas em diferentes locais tenham propriedades distintas, fato que pode decorrer da época em que tais amostras são coletada (NASCIMENTO *et al*., 2019), o que explica a discrepância entre os valores de Concentração Inibitória Mínima e de Concentração Fungicida Mínima encontrados nos diferentes estudos explorados, sugerindo grande variabilidade na atividade antifúngica do extrato de própolis vermelha (BOTTEON *et al*., 2021; SOKOLONSKI *et al*., 2021; MOREIRA *et al*., 2022). Portanto, além de poucos estudos acerca do referido tema, a origem biológica da própolis vermelha representa outro desafio à compreensão da sua ação fungicida.

Ainda, é importante lembrar que a própolis vermelha – por ser encontrada em diferentes estados do Brasil, assim como em diversos países do mundo – pode ter sua atividade antifúngica influenciada por fatores como temperatura, ciclos pluviais e locais de extração, afirmam Moreira *et al*. (2022). Reiteram ainda que, apesar das vantagens farmacológicas desse composto, sua baixa solubilidade em água – propriedade já descrita por Kubiliene *et al*. (2015) – pode impactar negativamente sua atividade antimicrobiana. Entretanto, como ponto positivo, Santos *et al*. (2021) afirmam que a própolis vermelha é uma substância natural que não apresentou efeitos colaterais ao combater fungos em seu modelo experimental, além de estar fortemente associada com a coibição da disseminação fúngica.

Nessa perspectiva, Sokolonski *et al*. (2021) evidenciam que a ação antifúngica da própolis vermelha pode ser superior em comparação às demais. Estes autores comprovaram que extratos de própolis vermelha apresentaram cerca de duas vezes mais flavonoides e formononetina quando comparados aos extratos de própolis verde, sugerindo que o alto teor desses compostos pode estar associado à melhor inibição do crescimento de *Candida ssp.* pela própolis vermelha frente à verde. Ainda, tais autores afirmam que a própolis vermelha aumentou em mais de dezesseis vezes a susceptibilidade ao fluconazol em culturas de *Candida parapsilosis*, *Candida glabrata*, *Candida krusei* e *Candida tropicalis*, todas anteriormente com maiores valores de IC50 a esses medicamentos. Entretanto, faltam estudos que observem outras propriedades da própolis vermelha, a exemplo de sua ação cicatrizante associada à atividade antimicrobiana e antifúngica, como já constatado em outros tipos de própolis (JULIÃO *et al*., 2023).

Além disso, foi possível visualizar na Tabela 2 a existência de apenas um ensaio clínico que tenha explorado a ação antifúngica da própolis vermelha. Nesse ensaio, pode-se verificar que a condição clínica contemplada relaciona-se unicamente com o uso odontológico da própolis vermelha, o que ressalta a importância da realização de mais estudos acerca do seu potencial antifúngico, com vistas a compreender suas possibilidades terapêuticas e sua aplicabilidade nos diversos campos das ciências da saúde.

5. CONCLUSÃO

O presente estudo permitiu vislumbrar que a ação antifúngica da própolis vermelha é uma das grandes potencialidades desse produto natural. Entretanto, foi evidenciado que o volume de estudos relativos a esse tema ainda é bastante incipiente e, somado à complexidade inerente desse composto, configuram-se como desafios à sua aplicabilidade. Contudo, os dados científicos explorados ao longo deste estudo comprovam o potencial da própolis vermelha em relação à sua ação antifúngica, fato este que pode auxiliar a sociedade em seu combate a formas resistentes destes microrganismos, assim como subsidiar pesquisas em sua incessante busca por produtos naturais de ampla aplicabilidade. Por esse motivo, espera-se que estudos futuros acerca da atividade antifúngica da própolis vermelha incluam a padronização das metodologias e dos extratos utilizados, além de ampliarem seus testes para mais espécies de fungos

além daquelas observadas nesta obra, com a finalidade de viabilizar comparações entre estudos visando à obtenção de um panorama mais fidedigno acerca da real ação fungicida da própolis vermelha. Ademais, é importante que sejam investigados seus efeitos sinergéticos em relação aos antifúngicos comerciais, corroborando a formulação de novas terapêuticas frente a tais microrganismos. Por fim, é relevante salientar que as limitações do presente estudo se encontram no fato deste não contemplar todas as bases de dados científicos existentes, de forma a ser possível que contribuições teóricas e práticas relevantes ao tema não tenham sido consideradas ao longo das discussões.

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