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A Comprehensive Literature Review on the Antineoplastic Activities of Chemical Constituents Isolated from Plants of the Clusiaceae Family

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Abstract

Cancer is a complex disease that drastically affects the patient's life in biological, behavioral, and socioeconomic aspects. Despite surgical procedures, cancer treatment involves the use of radiotherapy and drugs that often cause serious adverse effects. The search for new, more effective, and safe compounds is an ongoing event among several research groups, and medicinal plants represent an invaluable source of chemical compounds with different biological effects, including antineoplastic activity. This work aimed to perform an integrative review of the literature to search for the latest findings on the biological activity of different types of extracts and secondary metabolites of two genera of plants belonging to the Clusiaceae family in different experimental studies. The search for articles was carried out in the databases PubMed (NCBI), Virtual Health Library (VHL), Scientific Online Electronic Library (SciELO), Medical Literature Analysis and Retrieval System Online – MedLine (PubMed), Scientific Electronic Library – SciELO and Latin American and Caribbean Literature in Health Sciences – LILACS. Secondary metabolites found in plants belonging to the Clusiaceae family have anticancer effects that are evoked by different biochemical mechanisms, and studies on these metabolites deserve to be expanded, as these substances may represent an invaluable source of natural origin for the development of new drugs to be used in the treatment of cancer.

Keywords: Cancer, Neoplasms, Medicinal plants, Biological activities, antitumor activity

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1. Introduction

Brazil is the largest country in South America, covering millions of square kilometers, effectively making it the fifth-largest country in the world in terms of area. It has the largest tropical forest, large plains, mountainous areas, and a great diversity of flora and fauna [1]. Furthermore, it is the country with the greatest plant genetic diversity on the planet, with thousands of species of animals, plants, and fungi [2]. In this way, Brazilian biodiversity has been responsible for discoveries of substances that have led to innovations in the treatment of diseases worldwide, but despite this, its biological resources have not yet been fully explored [1]. The systematic search for organisms, genes, enzymes, substances, processes, and parts of living beings in general, is one of the ways to extract economic value from biodiversity [3]. This strategy can eventually lead to the development of a product with significant significance for humanity. Thus, biological prospecting encompasses many sectors such as agriculture, biotechnology, pharmaceutical and cosmetic industries, and health, among others [3]. In this context, the pharmaceutical industry, related to health and well-being, stands out for generating very high monetary values [4], with natural products representing more than half of the molecules approved as drugs in recent decades. Therefore, natural products continue to be a source of great importance, despite the very small number of the pharmaceutical industry

programs for drug discovery [5]. Among the various existing diseases, cancer is considered one of the main causes of mortality in the world, therefore characterizing itself as a serious and the critical global public health problem [6]. Over the decades, research carried out to search for and develop the substances with the anticancer activity has demonstrated the great contribution of substances of the natural origin in this sense [5].

1.1. Phytochemical profile of Clusiaceae – genera Garcinia and Clusia

The Clusiaceae family is an important source of secondary metabolites, such as anthraquinones, anthrones, benzophenones, coumarins, flavonoids, xanthomes, and triterpenes [7]. Several species of this family have activities: anti-inflammatory, anti-infectious and anticancer, antinociceptive, antioxidant, antidiabetic, antimicrobial, and hepatoprotective, among other pharmacological activities [8-11]. This family has approximately 15 genera and 800 species, distributed throughout the different tropical regions of the world [12], and are characterized by shrubs and trees; some species are hemiepiphytes. In Brazil, it is possible to find 12 genera and 147 species of Clusiaceae [13]. The genus *Garcinia* has approximately 240 species [12-13], distributed in Southeast Asia (e.g., *G. cambogia*, *G. dulcis* and *G. mangostana*), India (e.g., *G. indica*), Africa (e.g., *G. kola*) and South America (e.g., *G. humilis* and *G. brasiliensis*) [14]. The fruits of this genus plant are edible and used in agriculture and their seeds are used in the production of dyes or oils, as antioxidants, or in the treatment of various diseases such as hyperglycemia, diabetes, and cancer [15-17]. There are several classes of substances in *Garcinia* species, such as xanthones [18], procyanidins [19], bisflavonoids [20], and phloroglucinols [21].

The species of this genus present a wide variety of biological activities, among which the anticancer activity stands out [9-11-17-21]. In China, gamboge resin, extracted from *Garcinia* species, is rich in xanthones and used in oral and injectable formulations to treat breast carcinoma and malignant lymphoma [22]. These xanthones have aroused much interest due to their cytotoxic activity in several tumor cell lines, even at low concentrations. Furthermore, these substances often do not present multidrug resistance (MDR), an important property for chemotherapeutics, and for these reasons they are considered promising possible anticancer agents [23]. Different xanthones were isolated from the stems of *Garcinia schomburgkiana* and three of these xanthones showed cytotoxicity against four tumor cell lines (KB, HeLa S3, MCF-7, and Hep G2), with IC50 values in the 0.18-9.95 μM [24]. In the same way garcinol, a polyisoprenylated benzophenone, is isolated from the fruits of *Garcinia indica* and has anticancer properties involving different targets, demonstrated by many *in vitro* and *in vivo* studies [25]. Recent studies suggest that garcinol is a histone acetyltransferase (HAT) inhibitor and a microRNA (miRNA) disruptor, which acts in the development and progression of several types of cancer.

This HAT and miRNA modulating action indicates an epigenetic potential [26]. Another genus of the Clusiaceae family, also widely studied, is the genus *Clusia*, which has hundreds of species and a wide geographical distribution [12]. The total distribution of this genus extends to the north and south of the tropics and in Brazil, dozens of species can be found [27]. The chemical profile of *Clusia* species presents polyprenylated benzophenones [28-30], xanthones [31], biphenyls [32], flavonoids [33-34] and triterpenoids [35] and the anticancer activity in *Clusia rosa* is related to the presence of these polyprenylated benzophenones, which develop their biological effects by acting on topoisomerase activity [36]. Other studies on the anticancer activity of *Clusia* species have already been described [37-40] and will be detailed and shown in this review. In this context, this study aimed to perform a comprehensive review of the main secondary metabolites of the genera *Clusia* and *Garcinia* that present antineoplastic or anticancer activity and their respective modes of action in different types of cancer.

2. Methodology

The research is cross-sectional, exploratory, and descriptive, in which the bibliographic review method was chosen. For the survey, queries were made in the databases PubMed (NCBI), Virtual Health Library (VHL), Scientific Online Electronic Library (SciELO), Medical Literature Analysis and Retrieval System Online – MedLine (PubMed), Scientific Electronic Library – SciELO and Latin American and Caribbean Literature in Health Sciences – LILACS, with the descriptors: Clusiaceae, antineoplastic activity, anticancer activity, medicinal plants, secondary metabolites. The most appropriate combination of descriptors was used to achieve the proposed objective. In the screening, for the selection of works, the following criteria were used: theme in question, documents in English, Portuguese, and Spanish, and articles published preferably in the last twenty years.

3. Results and discussion

3.1. Anticancerous activity of the genus Garcinia

The fruits of *G. mangostana*, *G. xanthochymus* and *G. cambogia* are used by East Asian people as food or to control obesity. In India, extracts of *G. xanthochymus* and *G. cambogia* are used to intensify the flavor of curry and *G. cambogia* extract is also used as an antiseptic to preserve food [41-43]. The main constituent of *G. mangostana* fruits is α-mangostin, which has anticancer and chemopreventive action, acting in the three different stages of carcinogenesis, which are called initiation, promotion and progression [44]. The chemopreventive action of substances is linked to cancer initiation stage, which involves the inhibition of phase I enzymes (belonging to cytochrome P450/CYP superfamily), responsible for the activation of carcinogens and subsequent induction of phase II enzymes (e.g., glutathione-S-transferase), which conjugate carcinogens with endogenous ligands to promote their elimination [45]. Indeed, it observed that α-mangostin inhibited emergence of preneoplastic lesions induced by 7, 12-dimethylbenzanthracene (DMBA) in an ex vivo culture assay of mouse mammary cells. Since activation by DMBA requires presence of phase I enzymes (CYP1A1, CYP1A2 and CYP1B1), this fact may possibly be linked to inhibition of these enzymes in cancer initiation stage [46]. In support of this hypothesis, α-mangostin treatment of SK-BR-3 breast cancer cells caused dose-dependent inhibition of aromatase (CYP-19) in these cells.

The SK-BR-3 cell line has high levels of aromatase (CYP-19), which is a rate-limiting enzyme in estrogen biosynthesis. Since estrogen plays a vital role in the development and progression of hormone-responsive breast cancer, the suppressive effect of α-mangostin on aromatase indicates its potential as a chemopreventive agent in breast

carcinogenesis [47]. The generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) can occur through endogenous and exogenous pathways, such as inflammatory processes, UV irradiation, mitochondrial respiratory chain, lipid peroxidation and environmental pollutants [48]. During normal homeostatic conditions, cells maintain the ROS/RNS balance at adequate levels through the action of enzymatic antioxidants, such as SOD, CAT and GPx, as well as through non-enzymatic antioxidants, such as GSH and uric acid [49]. When this balance is disturbed, cellular defenses are overwhelmed and the cell undergoes oxidative modifications of carbohydrates and proteins, DNA strand nicks and lipid peroxidation, which can lead to cancer. In this sense, the literature reports that α-mangostin has a protective effect in processes involving oxidative stress [50-53], and that mechanisms involved include the elimination of free radicals, the modulation of enzymes linked to oxidative stress and the attenuation of the inflammatory process, blocking the development of cancer, even in its initial stage [44]. During cancer promotion phase, cells with dysfunction in control of proteins that regulate cell proliferation and apoptosis can give rise to a nucleus of pre-neoplastic cells.

Studies carried out with α-mangostin showed that this substance could act, in micromolar concentrations, in this phase of cancer. The mechanism of action of this substance occurs by modulating main mediators of cell cycle, generating apoptosis, by blocking G1/S transition, resulting in the interruption of the cell cycle in the G1 phase in prostate cancer [54], melanoma [55], breast cancer [56] and pancreatic cancer [59]. In prostate cancer, its antiproliferative activity also involves the negative regulation of cyclins D1 and D3, phosphorylated Rb, and cyclin E [54]. This substance induces apoptosis of several tumor cell lines *in vitro*, as well as in tumor implant models in animals, through modulation of pro- and anti-apoptotic signaling molecules [58-59], selectively, with low toxicity to normal cells [60-62]. Subsequently, pre-neoplastic cells transform into neoplastic cells when they begin to have angiogenic properties, promoting invasion of cells & tissues, generating metastases, entering cancer progression phase. Suppression of angiogenesis mainly involves the modulation of expression of vascular endothelial growth factor (VEGF), stimulates proliferation, migration, and differentiation of endothelial cells to form new blood vessels. VEGF binds to its receptors, generating conformational changes in receptors, dimerization, and autophosphorylation of tyrosine residues, activating signaling cascade such as MAPK and PI3K/Akt pathway [63].

The substance α-mangostin reduced the expression of VEGF in T47D breast cancer cells [64], thus inhibiting their progression. Furthermore, this xanthone is capable of preventing the progression of hypoxia-induced pancreatic cancer, which is also associated with angiogenesis [65]. Tumor cell invasion through the tumor-associated stroma and subsequent metastasis are the central events that occur in neoplastic progression. One of the crucial pathophysiological events of tumor invasion and migration is the excessive degradation of the extracellular matrix mediated by proteolytic enzymes, mainly MMP-2 and MMP-9. Thus, the literature reports that the xanthone α-mangostin can downregulate the expression of MMP-2 and MMP-9 in a dose-dependent manner, blocking the invasion and metastasis of different types of cancer, such as skin carcinoma [66], head and neck squamous cell carcinoma [67], lung adenocarcinoma [68], prostate carcinoma [69] and pancreatic cancer [70]. In addition to its ability to block, reverse, or delay carcinogenesis, acting at all stages through different mechanisms, α-mangostin also inhibits the activity of the ABC transporter, which is an interesting feature for chemotherapy, as it prevents MDR [71]. The literature also reports α-mangostin has chemopreventive, antiproliferative, pro-apoptotic, antiangiogenic, and antimetastatic properties against different types of tumor cells [72].

The substance garcinone E, another xanthone present in *G. mangostana*, shows cytotoxicity in several hepatocellular carcinoma cell lines [73] and inhibits the proliferation of pheochromocytoma (PC12) and glioma (U87) cells, with dose dependence, with this activity being more intense in glioma cells [74]. The anticancer activity of garcinone E is also observed in studies with colorectal (HCT-116), hepatocellular (HepG2), and breast (MCF-7) cancer cells. In this way, its antiproliferative effects against HCT-116 and HepG2 occur due to the interruption of the cell cycle in the G0/G1 phase and induction of apoptosis and necrosis, and the treatment performed with this xanthone in oral cancer cells (HSC-4) inhibits the proliferation of these cells and their colony-forming potential [41]. This antiproliferative effect of garcinona E is inherent to apoptosis and suppression of cell migration and invasion through inhibition of MMP-2 and MMP-9 expression [41]. Literature also reports that garcinona E is capable of causing a reduction in IL-6 production and an increase in IL-2 production, suggesting garcinona E has anti-inflammatory and immunostimulatory activity, which dectly contributes to its antimetastatic potential [75]. The growth of two other types of ovarian cancer cell lines (HEY and A2780) is also inhibited by treatment with garcinona E, through modulation of endoplasmic reticulum (ER)-induced stress and the (IRE)-1α signaling pathway, which reduces apoptosis via arrest of the cell cycle in the G2/M phase.

Thus, the process of cell invasion, based on modifications in MMPs and directly related to metastasis, is blocked [76]. Garcinone E also exhibits potent cytotoxic activity in cervical cancer cells (HeLa), and this effect involves the induction of apoptosis by arresting the cell cycle in the G2/M phase. Furthermore, this xanthone is also capable of suppressing cell migration, invasion, and adhesion [77]. In addition to garcinone E, several other prenylated xanthones have also been isolated from *G. mangostana* (e.g., 8-deoxygartanin, gartanin, 9-hydroxycalabaxanthone, and tovophyllin A). All of them showed antiproliferative activity against gastric (SGC 7901), cervical (HeLa), and hepatoma (HepG2) cancer cells, with garcinone-E having the most intense cytotoxic effect. Substitution of isoprene units in the A and B rings in combination with a 4-oxo substitution are determinants of antiproliferative activity, while cyclization of the isoprene unit causes a decrease in this activity [78]. Garciniaxanthone I and five other known substances isolated from bark of *G. xanthochymus* and tested in 4 tumor cell lines: hepatoma (HepG2), lung adenocarcinoma (A549), gastric cancer (SGC7901), and breast cancer (MCF-7) [79]. The results obtained in this study allowed us to conclude that garciniaxanthone I promote apoptosis in hepatoma cells (HepG2) via the mitochondrial pathway, mediated by caspases 3/7/9, increasing expression of the Bax gene (pro-apoptotic), with a reduction in the expression of apoptosis suppressor genes (Bcl-2, Bcl-XL, Mcl-1).

Treatment with this substance also inhibits expression of matrix metalloproteinases (MMP-7 and MMP-9), which are enzymes that degrade cellular matrix and linked to cell migration and metastasis [79]. Garcinoxanthocins A and B (Figure 1) and a glycosylated phenylpropanoid could be isolated from fruits of *G. xanthochymus*, in addition to seven other known substances, spiritone, 14-deoxygarcinol, xanthochimol, garcicovin C, isogarcinol, cycloxanthochimol and garcinialiptone. The anticancer activity of these substances evaluated against glioblastoma (U251MG) and breast cancer (MDA-MB-231) cells. Among substances, 14-deoxygarcinol presents greatest inhibition of U251MG cell proliferation, with an IC50 of 1.3 µM [80]. Substances garcinoxanthocins and B, xanthochymol, garcicovin, isogarcinol and cycloxanthochymol also have good antiproliferative activity, with IC50 values of 1.8–6.0 µM, while garcinialiptone has no antiproliferative activity. Furthermore, none of these substances affected cell viability of MDA-MB-231[80]. Treatment of glioma cells with xanthochymol inhibited phospho-tyrosine STAT3, suggesting that antiproliferative activity of this substance could be linked to inhibition of this protein since STAT-3 is an important target that controls cell proliferation and survival [80]. Garcicovin C inhibits migration of glioma cells and DNA binding activity of STAT-3.

Thus, xanthochymol and garcicovin C have a tumor-inhibitory effect related to the inhibition of STAT-3 in tumor cells [80]. The literature also reports that the substance 7-epiclusianone (Figure 2), isolated from *G. brasiliensis*, presents a concentration-dependent cytotoxic effect in A-549 cells, through induction of cell cycle arrest at the G1/S transition [81]. Furthermore, 7-epiclusianone was also tested in different cancer cell lines, such as melanoma (UACC-62), breast cancer (MCF-7) and drug-resistant breast cancer (NCI-ADR), non-small cell lung cancer (NCIH460), ovarian cancer (OVCAR 03), prostate cancer (PC03), kidney cancer (786-0) and tongue cancer (CRL-1624 and CRL-1623) and showed great antineoplastic biological potential [82]. The antiproliferative mechanism involved in 7-epilusianone's actions is related to inhibition of cathepsins B and G. These two enzymes are secreted by cancer cells and promote the hydrolysis of tumor cell's primary matrix, thus breaking the border with neighboring tissues and causing invasion and metastasis [82]. In this way, the viability of glioblastoma cell lines (U251MG and U138MG) is drastically inhibited when both treated with 7-epilusianone & this inhibition determines long-term effects, even after treatment is discontinued [82]. At low concentrations, treatment of glioblastoma cells with 7-epilusianone (10 µM) determines changes in cell cycle progression, implying a decrease in G2/M phase population. However, higher concentrations of 7-epiclusianone (40 µM) significantly increase the Sub-G1 population.

The results are compatible with the occurrence of apoptosis, but the mechanisms involved are different and require further studies [83]. Literature also reports that 7-epiclusianone is capable of inhibiting the growth of 60 cancer cell lines and inducing significant cell death in only a few cancer types, particularly renal cancer, melanoma, CNS tumors, colon cancer, and non-small cell lung cancer (NSCLC) [84-85]. Among the NSCLC cell lines, the cell line most susceptible to 7-epiclusianone is NCIH460, which originates from pleural fluid and was chosen for studies on the mechanisms involved. Cell cycle analysis revealed that cell death is preceded by an arrest in the G1/S phase, similar to what occurred in A549 lung cancer cells [81], suggesting that same mechanism of action may be involved, involving apoptosis in a concentration-dependent manner, where concentrations lower than 200 nM are capable of significantly inhibiting cell invasion [84]. Furthermore, 7-epi-clusianone at a concentration of 20 µM significantly reduces tube formation in human umbilical vein endothelial cells. This step is critical for the process of angiogenesis and is involved in both wound healing and tumor growth. In this way, 7-epi-clusianone possibly acts to inhibit continued tumor growth and metastasis of the NCIH460 cell line and displays excellent immunomodulatory activity [84].

3.2. Anticancer activity of the genus Clusia

Clusianone (Figure 3) is a polyisoprenylated benzophenone, an isomer of nemorosone, which was isolated for the first time from the roots of *Clusia congestiflora* [86]. The nemorosone (Figure 3) and clusianone enantiomers, as well as other pairs of polycyclic prenylated acylphloroglucinol (PPAP) enantiomers, were synthetically obtained to perform cytotoxicity tests of each pure enantiomer against different tumor cell lines [86]. The results obtained for treatments with the nemorosone and clusianone enantiomers are similar for cervical carcinoma (HeLa), pancreatic carcinoma (MIA-PaCa2), and breast cancer (MCF7) cell lines. Nemorosone enantiomers have activities very similar to those of clusianone [87]. Studies have shown that nemorosone acts by dissipating the mitochondrial membrane potential and releasing Ca^{2+} and high levels of cellular stress [88]. Thus, similarity between the clusianone and nemorosone isomers is due to their comparable physicochemical actions on mitochondrial membrane [87].

This action on mitochondria demonstrated in a study carried out with isolated rat liver cells (HepG2) where treatment with clusianone and nemorosone promoted protonophoric mitochondrial uncoupling, through the dissociation of phenolic protons in the mitochondrial matrix. This event evidenced by dissipation of the mitochondrial membrane potential and inhibition of Ca^{2+} influx, promotion of efflux in Ca^{2+}-loaded mitochondria, and decrease in ATP and NAD (P) H levels and generation of ROS [89]. However, the cytotoxic action and uncoupling of clusianone were considerably lower than those of nemorosone, probably due to an intramolecular hydrogen bond, which reduces the interaction with receptors [89]. Nemorosone, isolated from *Clusia rosea* floral resins, exhibits cytotoxic activity in epithelial carcinoma (HeLa), squamous cell carcinoma (Hep-2), prostate carcinoma (PC-3) and central nervous system carcinoma (U-251) cells [38]. This substance also determines *in vitro* cytotoxicity against breast, colon, ovarian, liver, and lung cells [36].

In Jurkat and K-562 leukemic cells, nemorosone determines antiproliferative and apoptotic effects, through inhibition of the Akt/PKB enzyme, promoting cell cycle interruption [39]. Furthermore, *in vivo* studies suggest that nemorosone significantly affects hematopoiesis in mice [94]. The literature also reports that nemorosone has a cytotoxic effect on neuroblastoma cell lines of the NB69, Kelly, SK N-AS and LAN-1 types, as well as on LAN-1 cells chemoresistant to cisplatin, etoposide, adriamycin, and 5-fluorouracil, and that in LAN-1 cells, this benzophenone causes an increase in cells in the G0/G1 phase and a decrease

in the percentage of cells in the S phase, with an increase in the levels of the p21Cip1 protein, one of main regulators of cell cycle arrest in the G1/S phase, evidencing presence of an apoptotic mechanism [40]. The effects of nemorosone on pancreatic cells (Capan-1, AsPC-1 and MIA-PaCa-2) differ from the mechanism of action in leukemic cells previously described [39], involving the release of cytochrome C from mitochondria and subsequent caspase-dependent apoptosis.

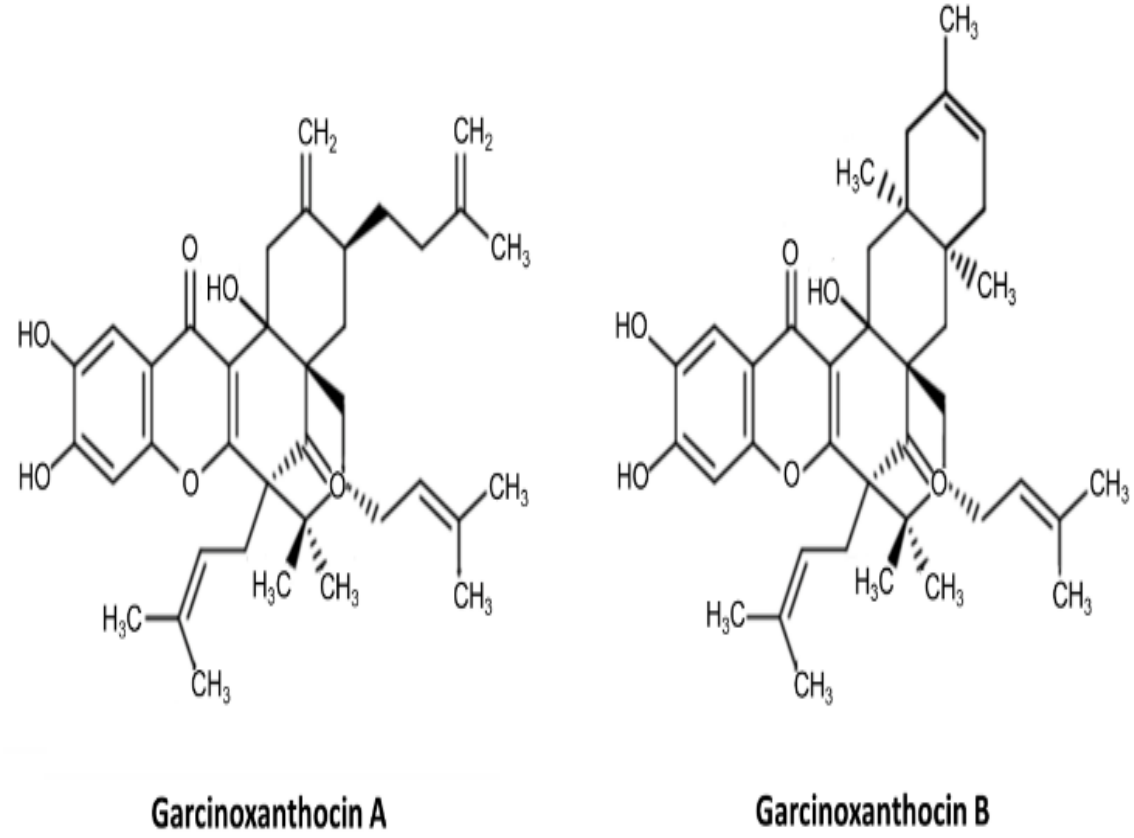


Figure 1. Molecular structures of xanthocins isolated from *Garcinia xanthochymus*

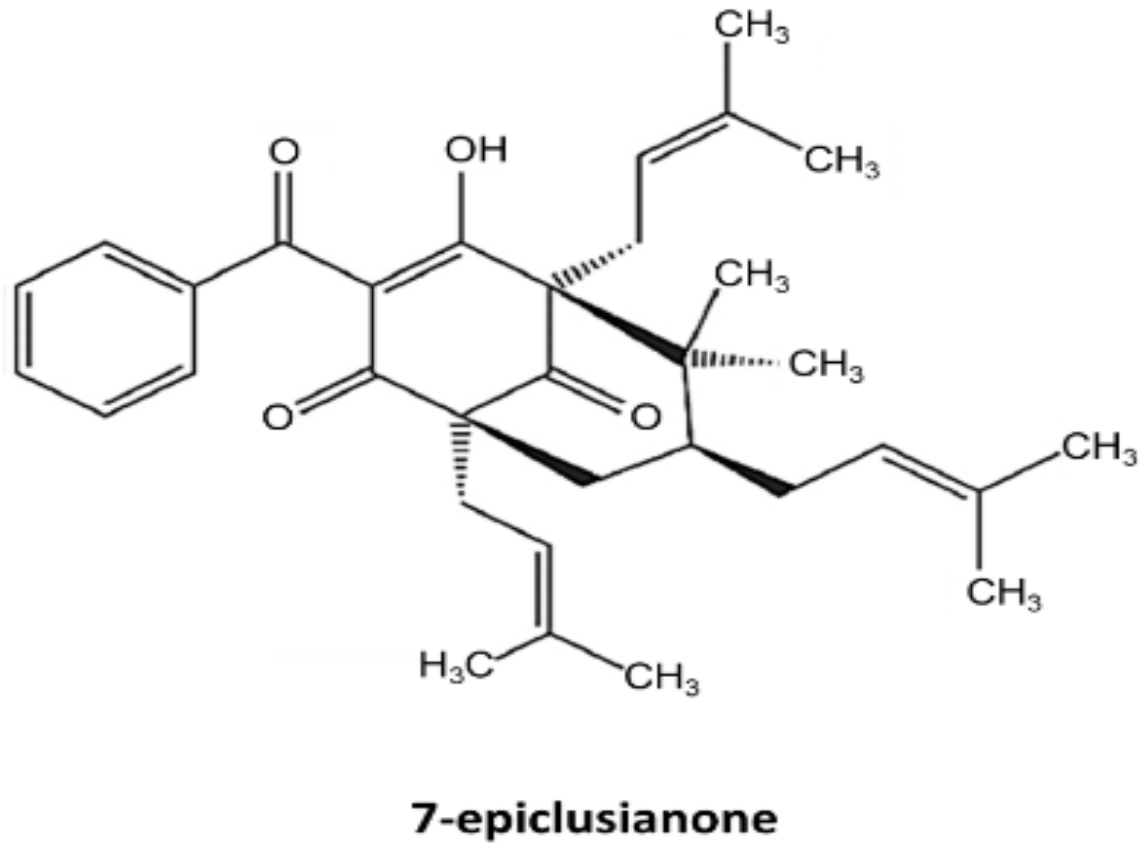


Figure 2. Molecular structure of tetraprenylated benzophenone isolated from *Garcinia brasiliensis*

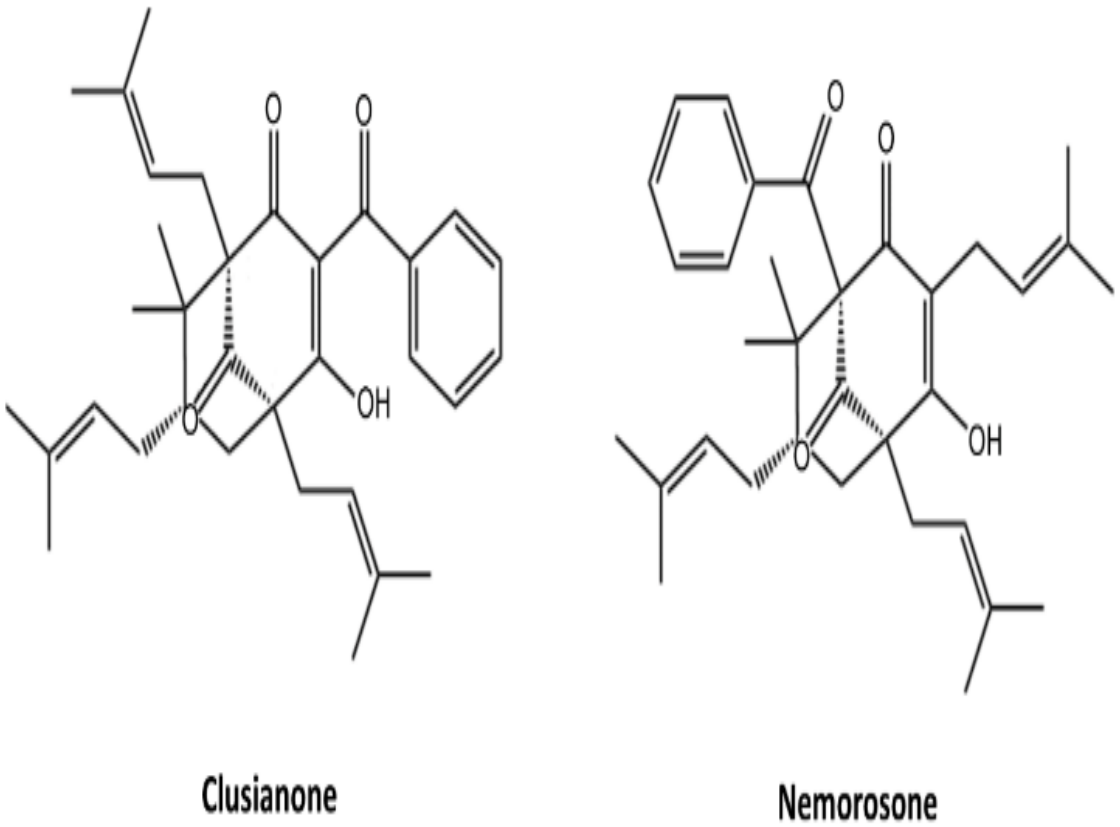


Figure 3. Molecular structures of two polyisoprenylated benzophenones isolated from *Clusia congestiflora*

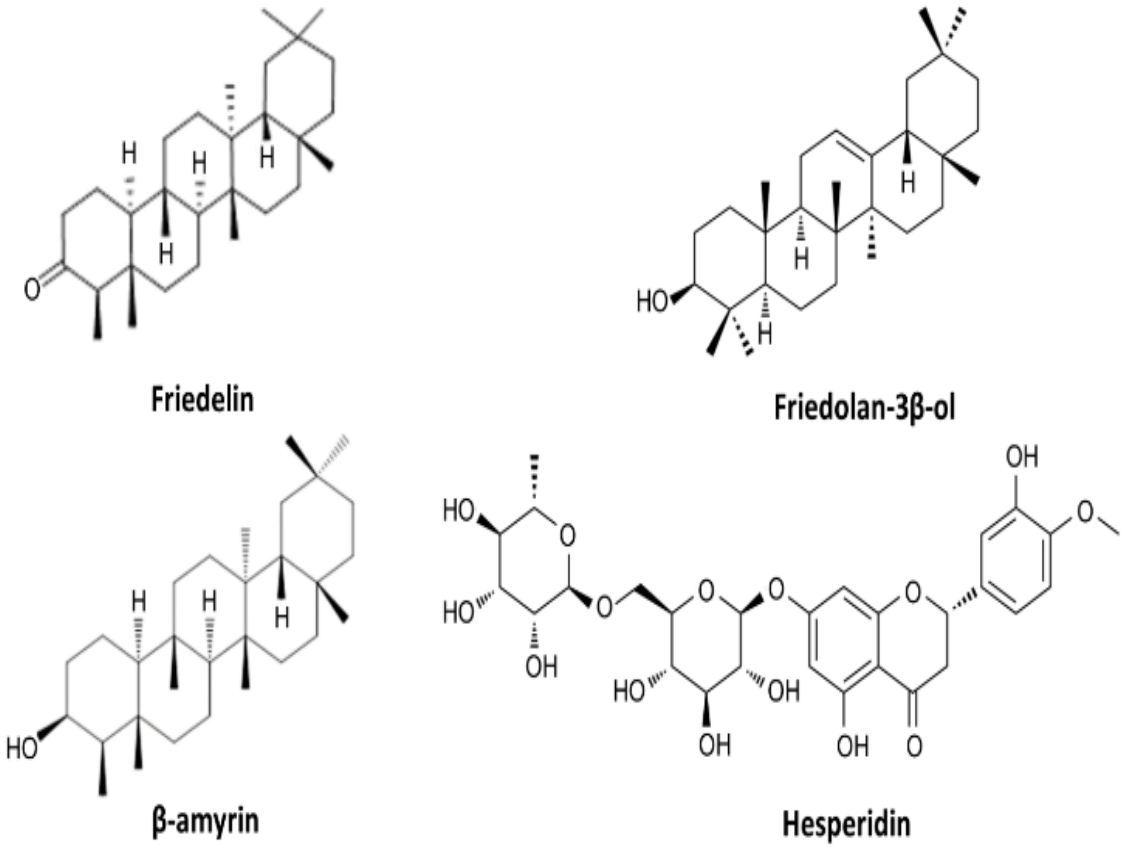
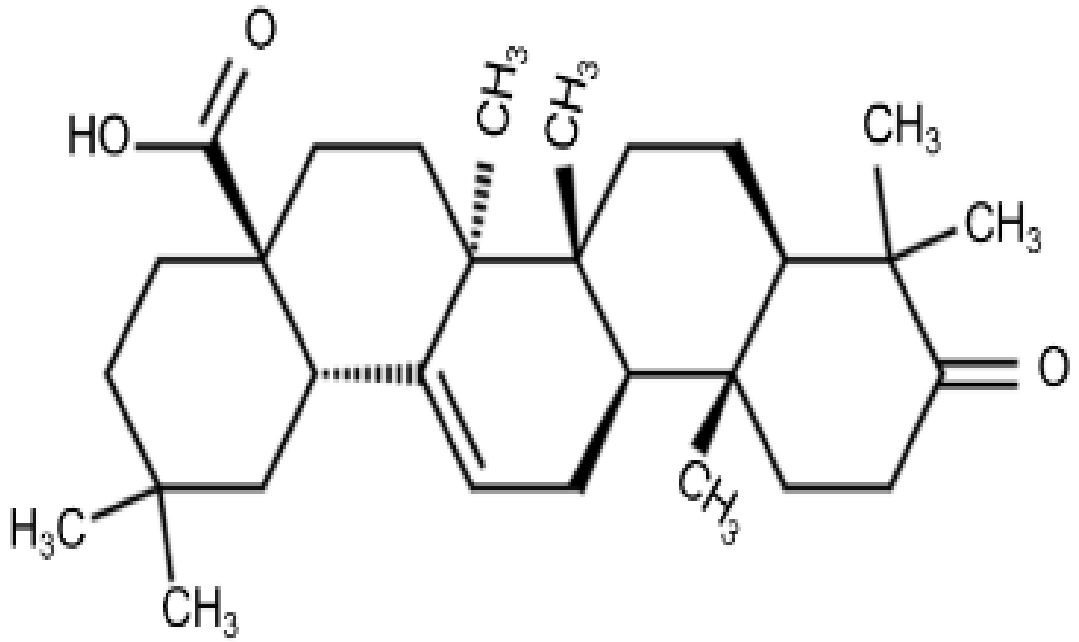


Figure 4. Pentacyclic triterpenes and a flavanone glycoside isolated from *Clusia latipes*



3-oxo-olean-12-en-28-oic acid

Figure 5. Molecular structure of a triterpenic acid isolated from *Clusia studartian*

Gene expression profiling revealed 336 genes affected by nemorosone. A total of 75 genes were altered in

all three cell lines, and many of them were within the unfolded protein response (UPR) network [90]. The UPR is triggered by accumulation of unfolded or misfolded proteins in endothelial reticulum (ER) and aims to restore cellular homeostasis, but triggers apoptosis if this is not achieved. In summary, anticancer mechanism of nemorosone in pancreatic cells is inherent in a rapid elevation of cytosolic calcium level, & depolarization of mitochondrial membrane, followed by activation of apoptosis, through a stress response pathway termed the UPR [90]. Nemorosone also exhibits antiproliferative activity against estrogen receptor-positive breast carcinoma cells (MCF-7) by arresting cell cycle in the G0/G1 phase. This antiproliferative effect appears to involve the interaction of nemorosone with estrogen receptors, since this effect is significantly reduced by 17β-estradiol and enhanced by estrogen receptor antagonism. Furthermore, nemorosone shows no activity against MDA-MD-231 tumor cells, an estrogen receptor-negative breast cancer cell line, and a prostate carcinoma cell line (LNCaP), suggesting that anticancer effects of nemorosone are dependent on its interaction with estrogen receptors [91-92].

Other studies on the anticancer mechanisms involved in these breast adenocarcinoma cells (MCF-7 BUS) showed that, in addition to the discreet arrest of the cell cycle in the G0/G1 phase, nemorosone causes significant depletion in the G2/M phase. Furthermore, nemorosone induces changes in the expression of 19 genes related to different pathways, especially the cell cycle, apoptosis, and hormone receptors [93]. As described earlier in this review, the cytotoxic effect of nemorosone against hepatic carcinoma cells (HepG2) acts through a mechanism that promotes the dissipation of mitochondrial membrane potential, through protonophoric uncoupling and activation of adenosine triphosphate (ATP) deflection [88]. In this way, studies carried out in HepG2 cells show that treatment with nemorosone significantly inhibits cell proliferation, both in the presence and absence of soluble factors secreted by tumor-associated macrophages (TAMs), with a reduction in number of colonies and cell migration [94]. Literature reports that cytotoxic effect of nemorosone on LoVo WT and LoVo Dox colon carcinoma cells (resistant to doxorubicin) is dose-dependent and time-dependent, and in addition to cytotoxic effect, nemorosone can restore sensitivity of resistant cell line to doxorubicin [95].

Furthermore, ROS production is significantly increased by nemorosone when compared to doxorubicin treatment alone, especially in resistant cells. This suggests that, in the induction of cell death, a synergistic effect of nemorosone and doxorubicin can be obtained and this synergism involves increased ROS production resulting in apoptosis by oxidative stress and drastic alteration of the membrane potential [95]. Nemorosone also has an anticancer effect on colorectal cancer (CRC) cells, reducing cell viability and clonogenic capacity through the induction of apoptosis with cell cycle arrest in the G0/G1 phase in a concentration-dependent manner. Nemorosone also reduces the expression of the BCL2 gene (anti-apoptotic) and intensifies the expression of the TP53 and BAX genes (pro-apoptotic), resulting in the activation of caspases 3/7 [96]. The literature also reports that this polyisoprenylated benzophenone attenuates cell migration and tumor invasion by inhibiting MMP9 activity, increasing E-cadherin (involved in cell adhesion), as well as decreasing the expression of β-catenin and vimentin, proteins involved in the epithelial-mesenchymal transition (EMT), thus decreasing the metastatic potential of CRC cells [96].

The cytotoxicity of twenty-five substances isolated from *Clusia criuva* extracts tested on human glioblastoma cells (GL-15). Unesterified betulinic acid, betulinic acid esterified by feruloyl at C-28, propolones B, C and D and hyperisampsin E showed greater cytotoxic potential than temozolomide, which is main chemotherapeutic agent used to combat proliferation of glioma cells (grade IV) [35]. Hexane, ethyl acetate, and methanol extracts of *Clusia latipes* also showed cytotoxicity against human prostate cancer cells (PC-3), colon cancer cells (RKO), astrocytoma cells (D-384), and breast cancer cells (MCF-7). In this context, the ethyl acetate extract showed more relevant cytotoxicity and the hexane extract showed genotoxic activity *in vitro*, evaluated by the comet assay [98]. Pentacyclic triterpenes such as friedelin, friedolan-3-ol and β-amyrin, as well hesperidin, a flavanone glycoside, (Figure 4), isolated from ethyl acetate extract isolated from hexane extract, present high cytotoxic activity, which may justify their possible anticancer potential [97]. Medicinal applications of Clusiaceae species have known for a long time, with emphasis on their antineoplastic activity.

Species *Clusia studartiana* has in its composition 2 pentacyclic triterpenes friedolan-3β-ol (Figure 4) and 3-oxo-olean-12-en-28-oic acid (Figure 5), and these secondary metabolites are capable of inhibiting the proliferation of myeloid leukemia cells (K562). However, only 3-oxo-olean-12-en-28-oic acid is capable of increasing the percentage of Annexin (V)/Propidium iodide (PI) in K562 cells, in addition to inhibiting the activity of P-gp. Thus, 3-oxo-olean-12-en-28-oic acid is a promising anticancer agent, even capable of preventing MDR [98]. The cytotoxicity of triterpenes is well described in literature. These substances inhibit cell proliferation and induce cell death through specific cancer targets, such as proteasomes, Bcl-2, NF-κB, TNF, STAT-3, TLR, PI3K/Akt/mTOR, and angiogenesis. Their anticancer mechanism consists of inhibiting inflammation and oxidative stress, regulating cell cycle by inducing apoptosis, and reducing cell proliferation [99]. Triterpenes stand out in research and development of new natural/semisynthetic anticancer therapies, particularly for treatment of sex hormone-dependent cancers (breast, ovarian, endometrial, prostate, and testicular), which related to high incidence of deaths worldwide. In these types of cancer, sex hormones maintain high mitotic rates and increase cell proliferation, increasing likelihood of genetic errors, disordered cell division, and malignant phenotypes [100].

4. Final considerations

Medicinal plants are essential for the development of new drugs for the treatment of cancer, as they can provide bioactive compounds that enhance the effectiveness of conventional pharmacotherapy. The Clusiaceae family represents an invaluable source of secondary metabolites that exhibit anticancer activity against different types of cancer. More detailed studies on the pharmacology of each substance described in this work may contribute to advancing the understanding of how these substances exert their anticancer effects and thus drive the discovery and development of new safe, effective, and natural drugs to be used in the fight against cancer.

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