Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2021; 10(2): 29-35
Received: 04-01-2020
Accepted: 18-02-2020

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Medicinal applications of *Euphorbia umbellata*, as an antitumor agent, antiulcerogenic and other applications: Review

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DOI: https://doi.org/10.22271/phyto.2021.v10.i2a.13669

Abstract
The demand for herbal medicines is steadily increasing. Within this perspective, compounds derived from the latex of the species *Euphorbia umbellata* have acquired a prominence presenting antiulcerogenic, anti-inflammatory, homeostatic activities and mainly antitumor activity. Studies carried out with tumor cells indicate that their fractions and subfractions act by modulating the apoptotic pathway by decreasing the mitochondrial electrical potential, as well as activating caspases 3 and 7. Concomitantly, its antiulcerogenic activity is related to the ability to capture radicals and species reactive oxygen, in addition to its inhibitory action in a peroxidase model. Other studies regarding other functionalities of this species are still in progress.

Keywords: *Euphorbia umbellata*, bio extracts, cancer

Introduction
Recently, the demand for herbal medicines and various natural products from a variety of plant species is steadily increasing. This immense importance within medicine is due to the fact that plants have been used for the treatment of various diseases for thousands of years, with extracts from various medicinal plants being effective against microbial, parasitic infections, inflammations, cancer, among several other applications [1, 2].
Of the total molecules approved for use in the pharmaceutical industry from 1981 to 2014, 52% are natural products or their derivatives [3]. Regarding cancer, for example, of all 131 molecules with antitumor potential released in the same period, 85 (49%) were derived from natural products and their derivatives, such as drugs such as Paclitaxel (Taxol®), Docetaxel (Taxotere®), Abraxane ® and Cabazitaxel (Jevtana®) [3, 4].
In turn, the species *Euphorbia umbellata* (Pax) Bruyns, of African origin and belonging to the order Geraniales, family Euphorbiaceae5. Popularly known as "Janaúba" and "cola-nota" in Brazil, it has already registered that its latex has been used in popular medicine as an anti-ulcer, anti-inflammatory, homeostatic, antiangiogenic, and mainly as an antitumor agent [6-8]. In southern Brazil, as well as common sense, it is used as a treatment for all types of cancer and has recently even shown molluscicidal activity to control schistosomiasis [9].

Family Euphorbiaceae
The Euphorbiaceae family corresponds to a botanical family distributed in 317 genera [10] with a total of 8,000 species present in the most diverse habitats, from humid tropics to arid regions, taken among the most economically important families in the Angiosperms group [11].
With the genera Euphorbia, Croton, and Phyllanthus being the most representative with respectively 1,500, 1,300, and 400 species, these plants have the most varied forms of life, such as herbs, shrubs, succulents, and trees with alternating leaves [12, 13]. Being the only family to present some species with a combination of glands and latex, generally recognized for exhibiting ciatio type inflorescence, unisexual flowers, and capsule type fruits [14-21].
In terms of industrial economic importance, *Ricinus communis* L., popularly known as castor, stands out, being a source of castor, an important product for the production of plastic, synthetic fibers, alternative fuel, among other applications. In addition to *Hevea brasiliensis*, which has its latex used for a natural rubber manufacturer [22].

Other species of this family are used for folk medicine, for their property in the treatment of hepatitis-B (antiviral activity), elimination of kidney stones (diuretic), and cancer, probably because they have several types of chemical compounds, such as flavonoids, saponins, terpenes, esters, cyanogenic glycosides, tannins, lectins, alkaloids, and glycoproteins [23, 24].

Species of the genera Croton and Mahinot were studied due to mineral absorption properties [25, 26]. The genus Croton is one of the largest genera of Euphorbiaceae most used in traditional medicine with several products derived from their species and commercialized on an international scale. Others of the genus *Euphorbia* L. and *Cnidosculus Pohl* have antidiarrheal effects [27]. The species *Euphorbia tirucalli* L. popularly known as "pau-pelado" or "avelós" for example, is traditionally used in Brazil as an analgesic, antitumoral, and antiviral [28].

In Brazil, in turn, is considered one of the most important research centers related to this family, more than 1,100 species [29], all of them native or acclimatized, with many of these species becoming objects of multidisciplinary studies from their characteristics, ethnobotanical and taxonomic importance, even biological properties, the majority medicinal potential [30].

Therefore, this work was developed through an integrative literary review, seeking to highlight the anti-tumor effects that *E. Umbellata* substances are capable of developing, as well as their applications and studies developed for other diseases.

Materials and Methods

The present work is characterized as an integrative literary review, seeking to study the aspects of *Euphorbia umbellata* as a phytotherapeutic agent, discussing its efficiency. For this, the Google Scholar, Scientific Electronic Library Online (SCIELO), and Pubmed platforms were used as a research base.

Development

Phytochemical studies

Several chemical metabolites have been detected in *E. Umbellata* latex since 1984 [31]. Premaratna *et al.*, isolated and purified lectins with antitumor properties [31]. Kinghorn (1980) discovered and isolated the 4-deoxy-starred ester, a product that causes skin irritability [32]. Other researchers, in turn, discovered the presence of diterpenes, protease enzymes, glycoproteins, and triterpenes [33, 36].

Likewise, its crude extract, as well as its diluted latex, shows antiulcerogenic activity in rats treated with this plant material, preventing the formation of peptic ulcers, in which such gastroprotective action was related to the presence of phenolic and non-saponifiable substances detected in its latex [37].

Later it was also verified through phytochemical studies the existence of lipophilic and phenolic compounds, starch, and mucilage. In addition to the isolation of two triterpenes identified using nuclear magnetic resonance (NMR) techniques, one being a pentacyclic called germanicol acetate and the other a tetracyclic called Euphol. In addition, other research has allowed the isolation of fractions and subfractions from the latex of this plant, such as fractions hexane, chloroform, ethyl acetate, and methanol and subfractions such as methanol, dichloride, ether, and ethanol [38].

In turn, the identification of the chemical composition of this plant is necessary because it is through it that it can be understood and attributed to the reason for its various therapeutic actions, through the action of primary and secondary metabolites that are present.

The class of secondary metabolites such as terpenes, alkaloids, and flavonoids has a promising anticancer activity [39-41]. Some terpenes and phenolic compounds are as promising, either because of an action directly linked or indirectly, such as that of phenolics that have proven antioxidant activity and may act to inhibit the development of the formation of free radicals, related to the progression of cancer [42, 43]. Some alkaloids in turn, such as those identified from *Catharanthus roseus (*L.*)* already present their active principles in drugs taken on the market such as vincristine and vinblastine [44].

Plant lectins also reveal themselves with heterogeneities appear mainly in their carbohydrate-binding sites, thus conferring multiple biological activities, among them potential as carcinogenic agents and recently in the discovery of tumor biomarkers, due to their ability to recognize a large number of glycans and mediate several biological processes, such as cell migration and immune defense [45].

It is also worth mentioning that the identification of bioactive compounds euphol, friedelin, and 3-friedelinol from the crude *E. umbellata* extract reinforced the idea that this plant is a source of antioxidant compounds, due to the marked action of the extract in chemical and enzymatic systems. (MPO) *in vitro*, as for the *ex vivo* system through hemolysis induced by free radicals, indicate a potential not only to neutralize but also to reduce the formation of free radicals, as well as to protect cells from its harmful action [46].

Antitumor potential

The crude ethanolic extract (EESU), its fractions chloroform, hexane, methanol, and its residual fractions chloroform (CF), hexane (HF) and methanolic (ME) had its antitumor activity tested in Ehrlich ascitic cells (EAT), decrease in cell viability *in vitro* by 50%, and inhibition around 75, 68 and 60%, respectively for the compounds CEE, CF and HF. In turn, *in vivo*, it was possible to observe better results for the crude ethanolic extract, where the dissipated mice had longer survival, 36.7% reduction in the intraperitoneal tumor cell load, and a 42% reduction in VEGF levels when compared to the control [47].

During the development of a tumor, it has been expanded that VEGF (vascular endothelial growth factor) is present in high definitions and plays a necessary role in increasing the permeability of specific vascularization in a variety of human animals and tumors [48, 49]. Therefore, it is important to determine the progression of the tumor and the induction of Angiogenesis [50]. Therefore, bioactive compounds that come to act in its demonstration reduction as a potent antitumor agent. In turn, in the same study, such compounds *in vitro* also demonstrated antitumor effects for k-562 [47] leukemic cells.

Another study also carried out with this cell line, Jukart cells (leukemic cell), HL-60 (Leukemic cell), HRT-18 (human ileocecal colorectal adenocarcinoma), and B16-F10 (murine melanoma cells), sought to evaluate *in vitro* the cytotoxic action of the compound euphol, a tetracyclic triterpene alcohol present in *E. umbellata*, showing that euphol has a cytotoxic effect mainly against leukemia potentially related to the apoptosis mechanism. However, the evaluation of the stability, distribution, and metabolism properties showed that euphol was unstable in gastric and intestinal fluids with an elimination half-life of two hours and possible phase II [51] hepatic metabolism, showing that *in vivo* such isolated

terpene has low cytotoxicity, which indicates that probably as anti-cancer properties of the extract may be caused by other substances present in the hexane fraction.

Hela cells (human cervical adenocarcinoma cells) and HRT-18 were also evaluated from tests with *E. umbellata* latex, where the latex cytotoxic application in HRT-18 cells after 48h and cytotoxic sensitization as Hela cells in all dose-dependent moments [52]. In turn, in subsequent studies, the cells and cells of Jukart cells undefined that the hexane fraction has a greater cytotoxic action, such action being associated with a possible trigger of cellular apoptosis [53].

In a biomonitored study to identify a more active fraction present in *E. umbellta* latex, methanol (MeOH), iso-propanol (iso-prop), ethyl acetate (EtOAc), chloroform (CHCl 3) en-hexane (Hex) were also evaluated. The results showed that all cytotoxicity fractions depend on concentration and time. It can also be assumed that for the three application methods, the hexane fraction has the greatest cytotoxic effect when compared to the chloroform (CHCl3), ethyl acetate (EtOAc), and methanol (MeOH) fractions, with a marked reduction in cell viability over time incubation of 24, 48 and 72 h for the hexane fraction for Hela, HRT-18 and Jukart cells, and the cytotoxicity of the hexane fraction for Jukart cells is related to the increased fragmentation of genetic material, cell death (apoptosis) and stopping the cell cycle in the g0/G1 phase with a reduction in the S and G2/M phases [54].

Such results of which mechanism of action *E. umbellata* acts can also be corroborated, through two other *in vitro* studies with the same cell line, in which for one of them Jukart cells through the cytotoxic action of the chloroform fraction (CHCl3) from the crude extract of the plant's bark, the cell cycle stopped and apoptosis, with the compounds present in CHCl3 presenting a greater amount of steroids and triterpenes55. And another showed that the dichloromethane subfraction from the hexane fraction indicated a promising result possibly due to the synergistic action of the terpenes present in it [56].

The action of steroids and terpenes has been previously described as promising, either directly or indirectly due to their antioxidant actions [42, 43], responsible for the reduction of free radicals that are normally present in a tumor microenvironment, showing them in large quantities and in excess related to several cellular dysfunctions [57]. In turn, recent studies show that the use of antioxidant compounds as part of the nutritional therapy of cancer patients has positive results in mitigating adverse effects generated by chemo and radiotherapy [58].

Another study also showed that fractions of terpenes enriched in *E. umbellata* latex promoted apoptosis in HL-60 leukemic cells, causing morphological changes compatible with the induction of apoptosis, altered cell cycle, depolarized cells, and the activation of caspase 3 and caspase 7 [59].

In general, caspase 3 mediates apoptosis by acting via the mitochondrial pathway [60] and terpenes activate caspase 3 activity as seen in tumor cells k-562, Hela, MCF-7 (breast cancer) and MDA-MB 231 (Breast cancer negative triple) [61]. And, likewise, caspase 7 is also an executor in which its enzymatic activity is necessary to complete cell death by apoptosis [62].

In turn, other studies carried out with tumor cells of murine melanoma B16-F10 showed that the hexane fraction, the petroleum ether subfraction, and dichloromethane showed potential *in vitro* but without significant results *in vivo* [63]. However, the chloroform and acetate fractions *in vitro* exhibited selective cytotoxicity when compared to normal human fibroblast (FN1) cells, reducing the mitochondrial electrical potential, modifying the cell morphology, and affecting the actin filaments, probably promoting the modulation of the apoptotic pathway [64].

The chloroform fraction and especially the acetate fraction also acted in reducing the mitochondrial electrical potential, as well as in stopping the cell cycle in the G2/M phase and reduced cell reduction in the G0/G1 phase. It also exhibits the same effect on MDA MB-231, 4T1 breast cancer cells, and Hepa1c1c7 [64-66] Hepatocarcinoma cells. The sub-fraction methanol (MeOH), derived from the hexane fraction, also responsible for reducing the mitochondrial electrical potential rm Hepa1c1c7 [67].

Such results indicate that there is an action of these fractions and subfractions with respect to a stop of the cell cycle, which is related to the control point (checkpoints) that guarantees the safety of the molecular structure of DNA, avoiding changes that cause harmful changes, genomic instability, and mutations that would be transmitted to the next cells [67-22]. As well as the decrease in mitochondrial electrical potential, it further supports the idea of a possible activation of apoptotic modulation of tumor cells through depolarization of the mitochondrial membrane. (Figure 1).

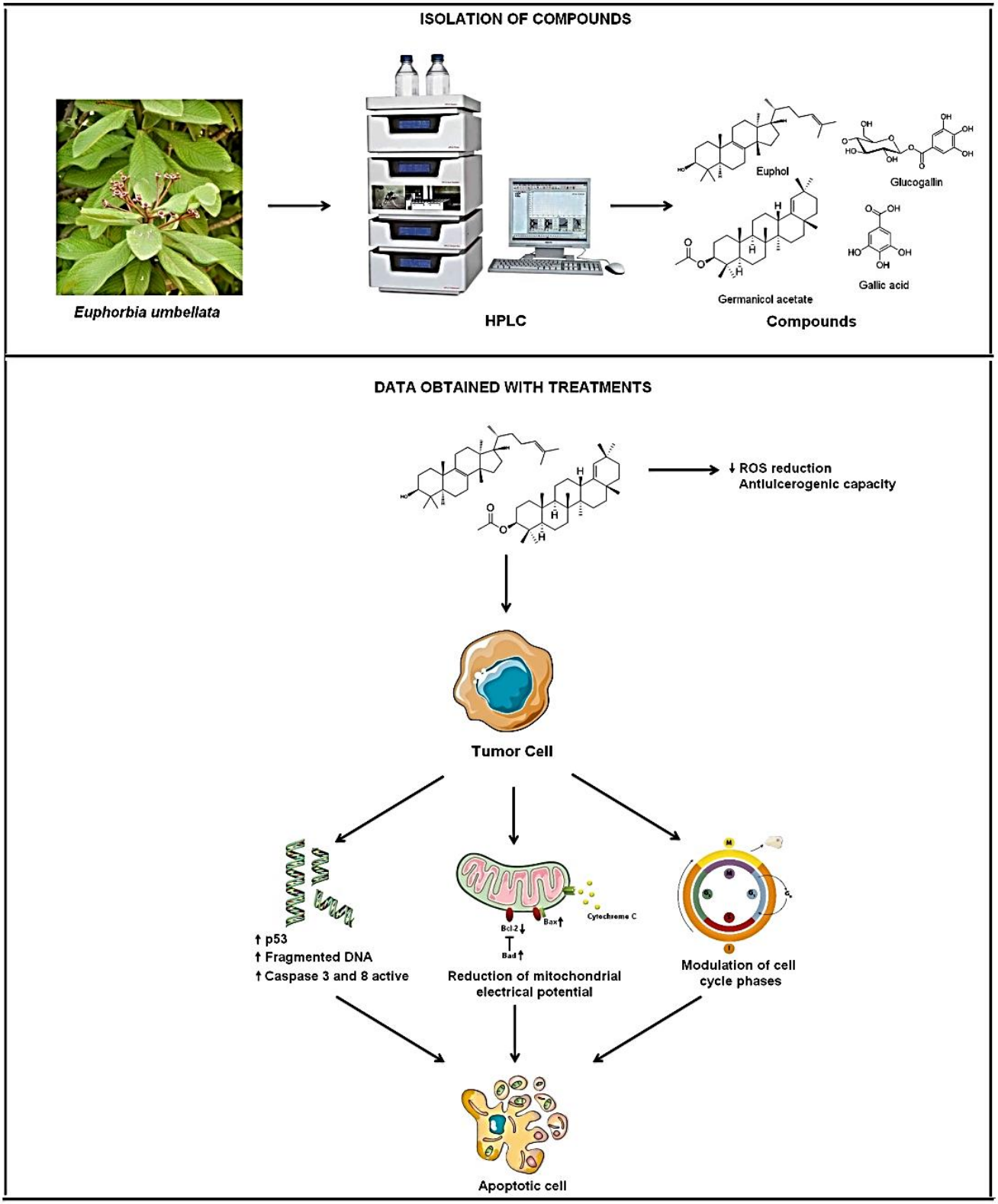

Fig 1: The action of compounds extracted from *E. umbellata* latex on tumor cells

Antiulcerogenic potential and other applications

To date, few studies have evaluated the pharmacological action of *Euphorbia umbellata* for the treatment of ulcers of the gastrointestinal tract. However, the few existing, existing that such a species has a promising potential.

The methanolic fraction (FM) from the *E. umbellata* peel had its antioxidant action tested against DPPH •, ABTS • +, O2 • -, HOCl, TauCl and HRP, where the responses in the antioxidant testicles are subject to the ability to capture radicals and reactive oxygen species by FM, in addition to its inhibitory action in a peroxidase model. In addition, histologically an FM provided gastroprotection and an enzymatic block presentation from the anti-urease test, allowing to suggest that the gastroprotective effect of FM may be related to the presence of polyphenols, as well as to its potential scavenger on reactive species, activation of the path nitric oxide/cyclic guanosine monophosphate and cyclooxygenases and anti-H actions. pylori and anti-urease [73]. Previously, Costa *et al*. also indicated that its crude and diluted latex promotes antiulcerogenic activity, preventing the formation of peptic ulcers in the food of rats treated by the action of phenolic and non-saponifiable substances [37].

Polyphenols, an example of flavonoids, are an important factor for gastroprotective activity and are substances that have been showing good activity against urease [74], acting in an antioxidant way and consequently contributing to anti-ulcer activity since urease, H. pylori and arginase are inhibitors of macrophage phagocytic function and are related to stimulating the activity of lymphocytes and neutrophils with a high production of ROS, which affects the transduction of signals from the gastric mucosal epithelium and allows the formation of neoplastic mass [75-78].

With regard to other applications, *E. umbellata* latex has the potential for obtaining molluscicidal agents that can be used to control schistosomiasis mansoni due to the presence of triterpenes [9]. In addition, chitosan membranes containing the *E. umbellata* methanolic fraction for topical application were developed, characterized, and evaluated for their antioxidant and antimicrobial potential, being considered promising for topical application for anti-inflammatory action [79].

In vitro experiments also induced that deoxy-phorbol esters present in the alcoholic extract of *E. umbellta* latex are able to increase HIV transcription and reactivate it from latency models and induce the production of pro-inflammatory cytokines together with interleukin-21, thus being promising candidates for future clinical trials aiming at the shock and deadly therapies that refer to HIV [80].

Conclusion

Like other species of the Euphorbiaceae family, a type *Euphorbia umbellata* has enormous pharmaceutical potential and can act in a beneficial way to fight various diseases. Other studies still need to be carried out so that it is possible to discover, in fact, which compounds are related to the most diverse pathogens, as well as their components of actions and consequences in the organism.

However, it is possible to notice an advance in studies with cancer cells when compared to other areas on the action of E. umbellata latex. It is possible to state that the various compounds from plant latex that have antitumor activity through the depolarization of the mitochondrial membrane, modulating the apoptotic pathway probably from the activation of caspases 3-7, operational for the cell cycle in the G2/M phase. Further studies are needed to specifically characterize the action of fractions and subfractions from latex.

With regard to its antiulcerogenic activity, it is related to the ability to capture radicals and reactive oxygen species, in addition to its inhibitory action in a peroxidase model. Regarding the other characteristics of this species, the studies are still chosen at an early stage.

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