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Phytochemical and pharmacological notes of plants indicated to treat tumors in Brazil

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Review

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Abstract: The plants used in traditional medicine have been considered an important source of molecules with pharmacological activity, including antitumor. The aim of this study was to present a pharmacological description and the phytochemical components related to antitumor activity of thirty plants commonly cited in Brazil to treat tumors as well as offering an overview of approaches that are necessary for the development of herbal medicines from these resources. In the search for studies with these plants, five database were used (SciELO, Scirus, Scopus, Biological Abstracts and Web of Science), with the following keywords: tumor AND Species AND cancer. We consider all the scientific synonyms of species available in the Tropicos® database (http://www.tropicos.org/). We surveyed papers from the period between 1980 and 2008. Twnety one species (70%) have at least one evaluation of a class of molecule or metabolite isolated against a pharmacological model. Most species (60%) has *in vivo* studies. Of the thirty plant species, two stood out for having pharmacological studies *in vitro, in vivo* and clinical with positive results: *Chelidonium majus* L., Papaveraceae, and *Aloe arborescens* Mill., Xanthorrhoeaceae. Although there is generally a good activity of species presented here, there is a need for further studies in order to evaluate the possibility of developing some byproduct.

Introduction

Brazil has a unique biological and cultural diversity that is reflected in a popular pharmacopeia very diversified, consisting mainly of medicinal plants (Melo et al., 2007). The record of popular uses of these plants has been performed by the ethnobotany, which has contributed both to nature conservation and for developing new industrial products (Oliveira et al., 2009).

Plants used in folk medicine have been considered an important source of molecules with pharmacological activity, including antitumor. Many studies have demonstrated that plants used in traditional medicine for treating cancer and tumors showed good pharmacological activity in vitro and/or in vivo using different experimental models (Ashida et al., 2010; Yang et al., 2007; Itharat et al., 2004).

This paper aims to lift the *state of art* of plants that are cited in ethnobotanical surveys to treat tumors in order to explain the existing gaps, as well as offering an overview of approaches that are necessary for the development of herbal medicines from these resources.

Materials and Methods

This work was based on a survey of ethnobotanical and ethnopharmacological studies developed in Brazil with medicinal plants. We used five database to rescue these works: SCIELO, SCIRUS, SCOPUS, Biological Abstracts and Web of Science. We used the following keywords: ethnobotany AND Brazil AND medicinal plants; ethnobotany AND Brazilian medicinal plants; Ethnopharmacology AND Brazil AND medicinal plants; and Ethnopharmacology AND Brazilian medicinal plants. We rescued works from the period between 1980 and 2008. From selected works, it was performed a detailed search for all plants that were cited in these studies and popularly referred as anti-

tumor. Subsequently, we conducted a further search of articles for each species, with the intention of rescuing the phytochemical and pharmacological works on them. All scientific names were checked and updated based on the Missouri Botanical Garden database (http//www.tropicos.org).

Results

We recorded 84 plants reported in the ethnobotany/ethnopharmacological literature that met our inclusion criteria. Below we summarize the studies on the anti-tumor activity of each plant species that we have found in our search. We succinctly describe pharmacological aspects of the thirty plant species which were reported in at least one study and molecules that have been isolated from them. For the other 54 plants we have not found works related to antitumor activity (see Melo et al., 2011).

Anacardium occidentale L., Anacardiaceae

Anacardic acid, a phytochemical component of this and other plant species, such as *Ginkgo biloba* and *Ozoroa insignis* (Sung et al., 2008; Rea et al., 2003), is a molecule of phenolic nature and is one of the major components of the fruit of this plant (Paramashivappa et al., 2001). Anacardic acid has cytotoxic effects against several cancer cell lines *in vitro* (Rea et al., 2003). In addition, anacardic acid sensitizes tumor cells to the cytotoxic effects of ionizing radiation (Sun et al., 2006). This molecule has proven to be a potent inhibitor of NF-κB activation, which likely explains its anti-proliferative, anti-angiogenic, pro-apoptotic and anti-metastatic effects (Sung et al., 2008). The polysaccharides, oligosaccharides, β-galactose and proteins present in the cashew resin of this plant have shown inhibitory activity against sarcoma-180 cells implanted in mice (Monthé et al., 2008). In a clinical study, Vicente and colleagues (Vicente, 2009) evaluated the use of a combination of *A. occidentale* and *Gliricidia sepium* extracts for the treatment of basal carcinoma in 37 patients. Upon topical treatment of the extracts over the lesion in the facial region, with an average of eight applications, it was found that 35 lesions were no longer detected during a routine exam between two to 84 months following the treatments.

Forsteronia refracta Müll. Arg., Apocynaceae

The substance extracted from this plant termed SL0101 is a kaempferol glycoside that inhibits proliferation of the human breast cancer cell line MCF-7 by inducing cell cycle arrest at the G1 phase through the action of the ribosomal S6 kinase (RSK) (Smith et al., 2005). This same molecule did not alter the proliferation of a control breast cell line (MCF-10A), although it did inhibit RSK in these cells (Smith et al., 2005). Other molecules belonging to the same class as SL0101 have been isolated from *F. refracta* and have also been shown to inhibit RSK (Xu et al., 2006).

Hancornia speciosa Gomes, Apocynaceae

The ethanol extract of the leaves of this plant exhibit anti-proliferative activity in different cancer cell lines *in vitro* (Endringer et al., 2009).

Himatanthus obovatus (Müll. Arg.) Woodson, Apocynaceae

The ethanol extracts of the leaves and roots of this plant exhibit cytotoxic activity against cerebrovascular, colon carcinoma, melanoma and leukemia cells *in vitro* (Mesquita et al., 2009).

Orbignya phalerata Mart., Arecaceae

The ethanol extract of the mesocarp/epicarp of this plant exerts cytotoxic effects preferentially in tumor cell lines when compared to non-tumor cells (Rennó et al, 2008).

Acanthospermum hispidum DC., Asteraceae

The methanol extract of the leaves of this plant exerts cytotoxic effects against lung (A-427), bladder (5637) and breast cancer (MCF-7) cells (Mothana et al., 2009). The ethyl acetate extract of the plant and its fractions exhibit anti-tumor activity in mice (Rajendran & Deepa, 2007).

Calendula officinalis L., Asteraceae

The laser-activated aqueous extract of *C. officinalis* flowers exhibit anti-proliferative activity in different cancer cell lines *in vitro*. The mechanism of inhibition of this extract was shown to involve cell cycle arrest at the G0/G1 phase and induction of caspase-mediated apoptosis (Jiménez-Medina et al., 2006). In addition, the extract also inhibits the growth of tumors *in vivo* (Jiménez-Medina et al., 2006). Two triterpene glycosides isolated from the flowers of this plant, calenduloside F 6'-*O*-*n*-butyl-ester and calenduloside G 6'-*O*-methyl ester, showed cytotoxic activity against colon cancer, leukemia and melanoma cell lines when used at concentrations below 20 μM (Ukiya et al., 2006).

Silybum marianum (L.) Gaertn., Asteraceae

Silibinin, a flavonoid present in the fruit of *S. marianum,* inhibits the growth and reduces the viability of three mouse prostate carcinoma cell lines (Tyagi et al., 2002). Treatment of the cell lines H-7 and I-8 with 100 μM of silibinin results in cell cycle arrest at the G1 phase when treated for 12 and 24 h and in arrest at the S phase when treated for 48 h (Tyagi et al., 2002). In addition, silibinin strongly inhibits DNA synthesis and induces apoptosis in these cell lines (Tyagi et al., 2002). Moreover, this molecule also has anti-proliferative activity in breast and ovarian cancer cell lines (Scambia et al., 1996). Silimarin, isolated from the fruit this plant, also exerts chemopreventive effects in skin and prostate cancer cells in several experimental models *in vivo* and *in vitro* (Deep & Agarwal, 2007). Bhatia et al. (1999) demonstrated that, when used in combination, silibinin and silimarin inhibit growth and DNA synthesis in breast, cervical and prostate cancer cells. These authors also suggest that the anti-tumor and chemopreventive activities of this combination treatment may be attributed to silibinin. Other studies suggest that both silibinin and silimarin are effective *in vivo* and *in vitro* for the prevention and treatment of cancer (Kim et al., 2009; Ramasamy & Agarwal, 2008; Agarwal et al., 2007; Hoh et al., 2007; Zhong et al., 2006; Chen et al., 2005; Davis-Searles et al., 2005; Singh & Agarwal, 2005).

Tabebuia impetiginosa (Mart. ex DC.) Standl, Bignoniaceae

β-lapachone, a quinone derived from the bark of this plant species, has shown significant cytotoxic activity against multiple myeloma (IC50 4-16 μM) and drug-resistant cell lines. In addition, this molecule can induce apoptosis in multiple myeloma cells (Gupta et al., 2002) and can inhibit growth and induce apoptosis in human colon and prostrate carcinoma cells (Lee et al., 2005). β-lapachone exhibits anti-metastatic and anti-invasive activities against human hepatocarcinoma cells (Kim et al., 2007). The β-lapachone in combination with ionizing radiation *in vitro* and *in vivo* produced more significant cytotoxic and anti-tumor (mice) effects than when administered alone (Park et al., 2006). Additional studies have contributed to our understanding of the mechanisms of action of β-lapachone (Lee et al., 2006; Woo et al., 2006; Choi et al., 2003a; Choi et al., 2003b).

Symphytum officinale L., Boraginaceae

The ethanol extract of the roots of this plant exhibit a 57.6% cytostatic (inhibition of mitosis) effect on human cervical epithelial carcinoma cells (Roman et al., 2008).

Carica papaya L., Caricaceae

5,7-Dimethoxycoumarin is produced by some plant species, including *C. papaya* (Alesiani et al., 2008). In the human melanoma cell line A375, this molecule exhibited cytostatic activity and blocked the cell cycle at the G0/G1 phase (Alesiani et al., 2008). Lycopene, a carotenoid also present in the papaya plant, has been shown to have anti-metastatic and anti-invasive activities in cancer cell lines and can inhibit the cell cycle and induce apoptosis (Breemen & Pajkovic, 2008). The *n*-hexane extract of papaya seeds induces apoptosis of the leukemia cell line HL-60 (Nakamura et al., 2007). Benzyl isothiocyanate, which is isolated from the fruit of this plant, exhibits cytotoxic activity against colon cancer cells (Miyoshi et al., 2006).

Maytenus ilicifolia (Schrad.) Planch., Celastraceae

Pristimerin, a triterpene isolated from the bark and root of this plant, exhibits anti-proliferative activity in HL-60 cells by inhibiting DNA synthesis and apoptosis (Costa et al., 2008). This molecule also induces apoptosis of prostate cancer cells (Yang et al., 2008). Shirota et al. (1994) isolated the aromatic triterpene 6-oxotingenol, which was shown to have cytotoxic activity against three different tumor cell lines (L-1210, P-388 and KB) when used at concentrations between 2.6 and 30 μg/mL. Erythrodiol, a terpenic compound isolated from the leaves of this plant, exhibits cytotoxic activity against KB/S cells when used at a concentration of 7 μg/mL (Ohsaki et al., 2004).

Chenopodium ambrosioides L., Amaranthaceae

The hydroalcoholic extract of wormseed leaves exhibits anti-tumor activity in mice (Nascimento et al., 2006). Ascaridol exhibits *in vitro* antineoplastic activity in different tumor cell lines (Efferth et al., 2002).

Manihot esculenta Crantz, Euphorbiaceae

The aqueous extract of the leaves of this plant has cytotoxic activity against cervical and ovarian adenocarcinoma cells (IC50 57 and 38 μg/mL, respectively) (Yusuf et al., 2006). Linamarin, a cyanogenic glycoside isolated from this plant, combined with the linamarase enzyme is more cytotoxic against breast cancer, colon adenocarcinoma and leukemia cells than when pure or crude linamarin extract is used alone (Idibie et al., 2007). Two triterpenic acids, esculentoic acids A and B, exhibit cytotoxic activity against ovarian cancer cells and have IC50 values of 6.4 and 4.8 mg/mL, respectively (Chaturvedula et al., 2003).

Anadenanthera colubrina (Vell.) Brenan, Fabaceae

An acidic heteropolysaccharide isolated from the resin of this plant exhibits anti-tumor activity against solid and ascitic tumors in rats when administered at a dose of 100 mg/kg (Moretão et al., 2004).

Bauhinia forficata Link, Fabaceae

The HY52 substance, which as isolated from the leaves of this plant, inhibits the growth of cervical adenocarcinoma cells (IC50 0.11 µM) and induces apoptosis by promoting cell cycle arrest at the G1 phase (Lim et al., 2006).

Copaifera langsdorffii Desf., Fabaceae

Kaurenoic acid, a diterpene isolated from the oil/resin of this plant, inhibits the growth of leukemia (95.3%), breast carcinoma and colon cancer cells (47.5%) when used at a concentration of 78 µM (Costa-Lotufo et al., 2002).

Copaifera multijuga Hayne, Fabaceae

The hexane and chloroform fractions of the oil extracted from this plant exhibit anti-neoplastic activity in mice (Gomes et al., 2008). In addition, the resin oil and its fractions exhibit anti-tumor activity against a melanoma cell line *in vivo* and *in vitro* (Lima et al., 2003).

Senna occidentalis (L.) Link, Fabaceae

The ethanol extract of the leaves of this plant has selective cytotoxic activity against a central nervous system cancer cell line and has an IC50 of 3.9 µg/mL (Calderón et al., 2006).

Aloe arborescens Mill., Xanthorrhoeaceae

Clinical studies have demonstrated that cancer patients treated with a chemotherapeutic drug in combination with an extract of *A. arborescens* respond better than when treated with the chemotherapeutic alone (Lissoni et al., 2009). *A. arborescens* exerts a chemopreventive effect in hamsters with experimentally-induced pancreatic cancer (Furukawa et al., 2002). Aloin exhibits cytotoxic activity against a human colorectal cancer cell line and has an IC50 of 293.1±32.7 µM (Jin et al., 2005).

Aloe vera (L.) Burm. f., Xanthorrhoeaceae

Aloe-emodin (1,8-dihydroxy-3-[hydroxymeth yl]-anthraquione; inhibits cellular viability and induces apoptosis and cell cycle arrest at the G2 phase in human bladder cancer cells (Lin et al., 2006). In addition, this substance exhibits cytotoxic activity against neuroectodermal tumor cells *in vitro* and inhibits the growth of neuroblastomas *in vivo* (Pecere et al., 2000). It also inhibits proliferation and induces apoptosis of glioma cells (Acevedo-Duncan et al., 2004) and human gastric carcinoma cells (Chen et al., 2007). At a concentration of 10 µM, aloe-emodin exhibits anti-proliferative activity against the Merkel carcinoma cell line, which is an aggressive and rare type of sun-induced skin tumor that primarily affects elderly individuals (Wasserman et al., 2002). Aloctin I, a type of lectin isolated from the leaves of the *A. vera* plant, prevents tumor growth in mice when administered prior to tumor implantation (Akev et al., 2007).

Rapanea guianensis Aubl., Primulaceae

Rapanone (2,5-dihydroxy-3-tridecyl-1,4-benzoquinone, which is isolated from the bark of this plant, exhibits cytotoxic activity against breast, colorectal, larynx and gastric cancer cells when used at doses between 21 and 29.4 µM (Cordero et al., 2004).

Boerhavia diffusa L., Nyctaginaceae

The hydroalcoholic extract and an alkaloid (termed punarnavine) derived from this plant inhibit the metastatic progression of melanoma in mice (Manu & Kuttan, 2009; Leyon et al., 2005). In addition, the hydroalcoholic extract prevents skin carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA) in mice (Bharali et al., 2003). Moreover, several rotenoids isolated from this plant, including the boeravinones G and H, inhibit the activity of a breast cancer resistance protein (BCRP/ABCG2) (Ahmed-Belkacem et al., 2007).

Chelidonium majus L., Papaveraceae

Chelidonine, sanguinarine and chelerythrine, which are alkaloids isolated from this grass, induce cell death by apoptosis and/or necrosis in uveal melanoma cells (Kemény-Beke et al., 2006). Chelidonine induces cell death of pancreatic cancer cells via cell cycle arrest at prophase and metaphase (Gansauge et al., 2001). The ethanol extract of this plant exhibits anti-tumorigenic activity in mice with experimentally-induced hepatocarcinoma (Biswas et al., 2008). Ukrain, a semi-synthetic compound composed of triphosphoric acid and purified alkaloids derived from *C. majus*, which is a registered drug in Mexico and in some countries of the former Soviet Union, exhibits

cytotoxic activity against several tumor cell lines and has IC50 concentrations varying between 6.2 and 31.2 μM (Lanvers-Kaminsky et al., 2006). It also induces apoptosis of Jurkat T lymphoma cells (Habermehl et al., 2006). Clinical studies demonstrated that both treatment of advanced pancreatic cancer patients with ukrain alone or in combination with gemcitabine nearly doubled the average survival time of the patients (Gansauge et al., 2002). The nucleases isolated and purified from the sap of *C. majus*, referred to as CMN1 and CMN2, induce the apoptosis of HeLa cells when used at a concentration of 13.3 ng/mL (Nawrot et al., 2008).

Plantago major L., Plantaginaceae

The methanol extract of the leaves of this plant inhibit the growth of human breast adenocarcinoma and melanoma cells by 50% when used at a concentration of 46.5 μg/mL (Gálvez et al., 2003). In addition, treatment of ovarian and cervical carcinoma cells with 1 μg/mL of the methanol extract of the aerial parts of the plant reduce the cell numbers by 82% and 59%, respectively (Velasco-Lezama et al., 2006). Moreover, the aqueous extract of the plant exhibits anti-tumor activity in the Ehrlich's ascites tumor experimental mouse model (Ozaslan et al., 2007).

Plumbago scandens L., Plumbaginaceae

Several substances that exhibit cytotoxic activity have been isolated from *P. scandens*; however, plumbagin, which is isolated from the aerial parts of the plant, is the most studied. Plumbagin has cytotoxic activity against breast cancer and melanoma cells, with an IC50 of 1.28 and 1.39 μM, respectively (Nguyen et al., 2004). In addition, it inhibits the growth of epithelial cancer (Wish, IC50 21.2 μM), lung carcinoma (Calu-1, IC50 25 μM) and cervical carcinoma (HeLa, IC50 21.5 μM) cells (Lin et al., 2003). Plumbagin induces apoptosis and cell cycle arrest in a small-cell lung cancer cells *in vitro*, inhibits tumor growth *in vivo* (Hsu et al., 2006) and has activity against promyelocytic leukemia cells *in vivo* (Xu & Lu, 2009). It also significantly inhibits the growth of breast cancer cells and induces their apoptosis by inactivating NF-κB and Bcl-2 without affecting normal breast epithelial cells (Ahmad et al., 2008). Moreover, this molecule exhibits cytotoxic activity (IC50 14.6 μM) and inhibits microtubule polymerization in non-small-cell lung epithelial carcinoma cells *in vitro* (Acharya et al., 2008).

Psychotria ipecacuanha (Brot.) Stokes., Rubiaceae

Emetine works in synergy with doxorubicin, etoposide, oxaliplatin and docetaxel against three neuroendocrine tumor cell lines and it shows more cytotoxic activity than when emetine alone (Larsson et al., 2009). In addition, emetine induces apoptosis in some human tumor cell lines (Möller & Wink, 2007). Emetine has been evaluated for the treatment of solid tumors, but no significant regression was observed in patients who were treated with this compound during a phase II clinical trial (Zhou et al., 2005; Siddiqui et al., 1973).

Capsicum frutescens L., Solanaceae

Capsaicin and other carotenoids isolated from the fruit of *C. frutescens* exhibit cancer chemopreventive activity *in vitro* and *in vivo* (Maoka et al., 2001). Capsaicin has cytotoxic effects and induces apoptosis in a melanoma cell line (Jun et al., 2007). It also induces cell cycle arrest (G0/G1) and apoptosis in a squamous cell carcinoma cell line of the esophagus (Wu et al., 2006) and inhibits cell proliferation and induces apoptosis in human glioblastoma (Gil & Kang, 2008) and hepatocellular carcinoma cells (Jung et al., 2001). In addition, capsaicin inhibits the proliferation of pancreatic cancer cells and induces their apoptosis in vitro (IC50 150 μM) and *in vivo* (Zhang et al., 2008). Moreover, capsaicin inhibits the growth of prostate tumor cells *in vitro* (IC50 20 μM), suppresses their growth in vivo and induces their apoptosis *in vivo* and *in vitro* (Sánchez et al., 2006). Capsaicin also induces apoptosis of gastric cancer cells and normal cells, but the carcinogenic cells are more susceptible to the compound (Chow et al., 2007).

Solanum americanum Mill., Solanaceae

A 150-kDa glycoprotein isolated from the seeds of this plant exhibits cytotoxic activity and induces apoptosis in human colorectal carcinoma cells (Lee et al., 2004). *S. americanum*-derived polysaccharides have significant inhibitory activity against tumor growth in mice (Li et al., 2009; Li et al., 2007). In addition, the aqueous extract of this plant inhibits the growth of cervical carcinoma cells in mice by inducing cell cycle arrest (G0/G1) and apoptosis (Li et al., 2008). Solanine, an alkaloid, exhibits cytotoxic activity against human hepatocellular carcinoma cells (IC50 14.47 μg/mL) and induces their apoptosis (Ji et al., 2008). The ethanol extract of the ripe fruit inhibits cell growth and induces apoptosis of breast cancer cells (Son et al., 2003).

Viola odorata L., Violaceae

The acetone extract of *V. odorata* exhibits chemopreventive effects against DMBA-induced skin

cancer in mice (Perwaiz & Sultana, 1998). In addition, a macrocyclic peptide isolated from *V. odorata*, called cycloviolacin O2, exhibits *in vitro* cytotoxic activity against ten different cancer cell lines, including myeloma, leukemia, small-cell lung cancer, lymphoma and renal adenocarcinoma. It has an IC50 ranging between 0.1-0.3 μM and gives better results than the anti-tumor drugs currently in clinical use (Lindholm et al., 2002).

Conclusion

Although there is generally a good *in vitro* and/or *in vivo* activity of extracts, fractions or molecules isolated from brazilian medicinal plants popularly used for cancer, there is a need for further studies in order to assess the possibility of developing some by product.

We recommend that efforts are made to test hypotheses about effects observed (*e.g*, can compound A treat cancer? Did active compounds from B extract also show activity when isolated?). Thus, for plants that have only positive activity of extracts and/or fractions is necessary to elucidate the possible active compound(s) for further evaluation *in vivo*; and for plants with active molecules isolated with only *in vitro* and/or few *in vivo* studies are necessary a large number of pre-clinical studies to evaluate the efficacy and safety.

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