Review

Health and Diversity (Online), v.4, p.84-91, 2020
Centro de Ciências da Saúde – Universidade Federal de Roraima, Boa Vista, RR

ISSN 2526-7914

The anti-inflammatory and antitumor effects of medicinal plants: *Arctium lappa, Solanum torvum* and *Lobelia inflata*

Bárbara da S. Paschoal, Gabriela C. Carvalho, Gabriela Cauzzo, Vanessa L. Campo, Karina F. Zoccal, Cristiane Tefé-Silva*

Medical School, Barão de Mauá University Center - CBM, Ribeirão Preto, Brazil.

ABSTRACT

Introduction: Medicinal plants have been used since antiquity to treat illnesses and injuries. Considering their global use, many natural products have been investigated with the aim to get new drugs. **Methods:** The search was based on relevant articles indexed in PubMed, Scielo and Scopus. The search terms used were: medicinal plants, *Arctium lappa*, *Solanum torvum*, *Lobelia inflata*, anti-inflammatory effects, antimicrobial activity and antitumor effects. **Development:** *Arctium lappa* leads to the inhibition of nitric oxide synthase (iNOS) expression and nitric oxide (NO) production and inhibits the growth of some tumor cell lines. *Solanum torvum* can promote inhibition of inflammatory mediators release, and reduces the melanoma formation. *Lobelia inflata* can reduce the number of white blood cells, the TNF-α and IL-6 levels and the melanoma growth. **Conclusion:** The active principles present in these medicinal plants, including flavonoids and other phenolic compounds with antioxidant activity, can scavenge free radicals and therefore be effective against tumors, such as melanoma and skin cancer.

Keywords: *Arctium lappa*, *Solanum torvum*, *Lobelia inflata*, melanoma, skin cancer.

*Corresponding author: Cristiane Tefé-Silva
Medical School, Barão de Mauá University Center - CBM
Ramos de Azevedo 423, Ribeirão Preto, SP, Brazil.
CEP 14090-062
E-mail: cris_tefe@hotmail.com
Received: 28/09/2020 / Accepted: 27/10/2020

1. INTRODUCTION

Medicinal plants have been utilized since antiquity to treat illnesses and injuries. Several cultures throughout the mankind history have been using herbs and their derived compounds to treat diseases. According to the World Health Organization more than 80% of humanity still uses these resources (CASSILETH *et al*., 2001). Herbal medicines are among a comprehensive assortment of treatments referred to as complementary and alternative medicine (CAM) and have been used in several countries such China, Korea and Japan for thousands of years, and have the richest arrays of registered and relatively well-known medicinal plants (KALA *et al*., 2006). Plants have played key roles in the lives of indigenous peoples living in Brazil by providing forest products for both food and medicines.

Natural products, mainly of plant origin, are of utmost importance to get promising drug lead candidates and play an imperative role in the upcoming programs for drug development. Based on their global use, many natural products have been investigated as prototypes for the production of new drugs. In fact, approximately 80% of the anticancer, antimicrobial, immunosuppressive and cardiovascular drugs are primarily based on plant sources. Among 177 anticancer drugs, about 70% of the active molecules are based on medicinal plants (KUMARI *et al*., 2019; SEN; CHAKRABORTY, 2016). In fact, medicinal plants have gained wide appreciation due to their easy availability and low cost when compared to allopathic medicines. Owing to these advantages plant-based preparations have been selected as preferable choice among all available therapies.

However, many herbal products are still lacking scientific evidence of effectiveness and safety. Several studies have been described in literature about the adverse effects of different plants. Unfortunately, most herbal medicines that are currently used by self-medication or medical prescription do not have a well -known toxic profile (SILVEIRA *et al*., 2008).

Thus, this review describes an update of medicinal plants and their biological activities, with emphasis on the antimicrobial, anti-inflammatory and antitumor activities properties of *Arctium lappa*, *Solanum torvum* and *Lobelia inflata*.

2. METHODS

The search was based on articles indexed in PubMed, Scielo and Scopus from 1969 to 2020, with further emphasis on those indexed between 2005 and 2020. The search terms used were: medicinal plants, *Arctium lappa*, *Solanum torvum*, *Lobelia inflata*, anti-inflammatory

effects, antimicrobial activity and antitumor effects. The data disclosed in this review were collected from 72 articles and books. After the retrieved articles had been examined, relevant and eligible articles were included in the study.

3. DEVELOPMENT

3.1. Medicinal Plants

3.1.1. *Arctium lappa*

Among the known medicinal plants, stands out *Arctium lappa* (Burdock), which was brought from Japan and acclimated in Brazil, and has innumerable medicinal properties such as diuretic, laxative and antioxidant actions, besides acting as antiplatelet aggregation agent (PEREIRA *et al*., 2005; IWAKAMI *et al*.,1992). The main active components that can be extracted from this plant are: arctiin, arctigenin, tannin, inulin (CHAN *et al*., 2011), L-asparagine (URAZOVA *et al*., 2011), among others. Arctiin is the major lignan of *A. lappa* and it has a variety of important pharmacological properties, including antimutagenic (SHINOHARA *et al*., 1988), anti-inflammatory and antiviral activities (ZHOU *et al*., 2018).

In a study described by Yari *et al*., (2018), another characteristic of the plant was demonstrated, which is the more expressive antiradical activity of its extract when compared to vitamin C (ascorbic acid), since at the same dose, *Arctium lappa* extract outperforms vitamin C free antiradical activity by 16%. Thus, its medicinal significance can be justified based on the existence of various bioactive secondary metabolites, including lignans, flavonoids, caffeoylquinic acid derivatives and polyphenolic compounds (FERRACANE *et al*., 2010), which represent strong free radical scavengers, being considered good sources of natural antioxidants.

The antioxidant effect of *Arctium lappa* is due to inhibition of induced nitric oxide synthase (iNOS) expression and nitric oxide (NO) production, besides suppressing pro-inflammatory cytokine expression, inhibiting nuclear factor-kappa B (NF-κB) pathway, activating antioxidant enzymes and eliminating free radicals (CHAN *et al*., 2011).

The extracts from different parts of the plant help to strengthen the immune system, besides increasing the organism metabolic functions (CHAN *et al*., 2011). It has been proved that leaf parts and powdered stem of *A. lappa* revealed to have antioxidant effect (YARI *et al*., 2018), whilst its root seems to have active principles that promote the skin surface circulation, contributing to its better quality and texture, in addition to eliminating heavy metals from the body (CHAN *et al*., 2011).

Although some side effects have been demonstrated stemming from the long-term use of *A. lappa*, the most common are contact dermatitis and redness (RODRIGUEZ *et al*., 1995), and anaphylaxis, for which only one case was described (CHAN *et al*., 2011).

3.1.2. Anti-inflammatory effect

It is known that anti-inflammatory drugs express their effects by suppressing the enzyme cyclooxygenase (COX), culminating in the inhibition of the pro-inflammatory prostaglandins production. However, the continuous use of anti-inflammatory drugs triggers a series of gastrointestinal problems; therefore, new researches are being developed in order to identify natural compounds that can achieve the same anti-inflammatory effects without causing the undesired side effects (LEE *et al*., 2011).

Whereas inflammation and viral reaction are both caused by activated inflammatory and immune cells like macrophages and monocytes, the lignan arctiin has proven to suppress COX-2 expression, to inhibit PGE2 production and to down-regulate pro-inflammatory cytokines such as IL-1β, IL-6 (interleukin) and TNF-α (Tumor Necrosis Factor α) (LEE *et al*. 2011), improving anti-inflammatory and antiviral activities. Also, this lignan has shown activities like anticarcinogenic (HIROSE *et al*., 2000) and platelet activating factor (PAF) antagonism (IWAKAMI *et al*., 1992). However, there is another lignan, called arctigenin, that promotes major cytotoxicity when compared to arctiin (MORITANI *et al*., 1996).

Regarding the anti-inflammatory activities, it has been shown that arctiin promotes protective effect in cases of glomerulonephritis involving glomerular damage and renal function impairment. This compound works by ameliorating the symptoms of the aforementioned disease mainly through the suppression of NF-κB p65 activation and by decreasing pro-inflammatory cytokines levels, such as interleukin 6 (IL-6) (WU *et al*., 2009).

Arctigenin acts similarly to arctiin regarding anti-inflammatory activity, since it strongly inhibits NO production and iNOS expression, by suppressing NF-κB activation. This lignan also inhibits pro-inflammatory cytokines expression, as IL-6 and TNF-α, emphasizing its anti-inflammatory effect (CHO *et al*., 2002).

3.1.3. Anticancer activity

In general, during tumor development cancer cells are known to have the intrinsic capacity to tolerate extreme conditions, such as low nutrient levels and oxygen supply. Nevertheless, the compound arctigenin showed cytotoxicity in glucose and oxygen-deprived tumor cells (AWALE *et al*., 2006), bypassing such cells' ability to survive in hostile environments. In the same way, it is also known to inhibit the growth of various cancer cells such as those found in the lungs, colon, stomach and liver (HE *et al*., 2018). The effects of arctigenin on those types of cancer are due to its capacity to regulate extrinsic and also intrinsic apoptotic cell death in tumor cells (HSIEH *et al*., 2014). Moreover, arctigenin is able to regulate the expression of metastatic proteins, such as matrix metalloprotease (MMPs) (LU *et al*., 2015), and the epithelial-mesenchymal transition, resulting in the control of tumor invasion and migration (VERVOORT *et al*., 2013).

Thus, arctigenin may represent an alternative treatment to chemotherapy, once it is capable to select metabolically stressed cancer cells, without affecting healthy tissues (GU *et al*., 2012).

It is known that, in association to other proteins, cyclin D1 acts in an expressive way promoting the G1-to-S phase transition of the cell-cycle through the tumor-suppressor retinoblastoma protein (RB) phosphorylation (SHERR, 1993). Thereby, cyclin D1 protein improves the growth of several tumoral cells types, such as osteosarcoma, lung, colorectal, breast prostate cancer and even melanoma (MATSUZAKI *et al*., 2008). According to what was stated above, *Arctium lappa* has a compound called arctiin that acts directly in cancerous cells. In this regard, arctiin causes

a down-regulation of cyclin D1 protein expression in a dose and time-dependent manner. Therefore, it is possible to infer that arctiin can become a gene-regulation agent in chemoprevention and chemotherapy (MATSUZAKI *et al*., 2008).

3.1.4. Antitumor effects in Melanoma

Melanoma is known as an aggressive and malignant tumor arising from the melanocytes and its main cause is the prolonged exposure to the ultraviolet radiation from the sun. Over the past 30 years, the incidence of cutaneous melanoma has increased rapidly and it has become responsible for the majority of skin cancer deaths (KARLSSON; SALEH, 2017; ROSKO *et al*., 2017).

Metastasis is the major problem to cancer therapy and is the most common cause of death among the affected patients (GEIGER; PEEPER, 2009). Nevertheless, for metastasis to occur, angiogenesis is required, which is essential for tumor migration and invasion, constituting a relevant control point in the cancer progression (FOLKMAN, 2002). Thus, the angiogenesis suppression represents an important strategy for cancer treatment, in the same way that protecting the cells against noxious substances may inhibit cancer cells proliferation (CHAN *et al*., 2011). In this regard, flavonoid-type antioxidants and some other active polyphenol antioxidants, which are found in burdock root, may be responsible for suppressing cancer metastasis (TAMAYO *et al*., 2000).

In the search for new treatments against melanoma, it was observed that the compound Lappaol F exhibits remarkable growth inhibition of different tumor cells lines, including melanoma´s (SUN *et al*., 2014). Besides that, the compound L-asparagine showed a high antimetastatic effect on melanoma B16 cells, despite not displaying significant activity towards the primary tumor. Furthermore, L-asparagine is able to increase the antimetastatic activity of cyclophosphane, partially by reducing its toxic effect in the organism (URAZOVA *et al*., 2011).

In a study carried out with *A. lappa* extract, it was demonstrated that the tumor cells implanted in Balb/c mice had their cellular inflammation reduced, as well as the tumor growth, after the injection of the root extract during 30 days. As a result of this study, tumor growth suppression was achieved by 38% in just 20 days, showing that the use of *A. lappa* extract may be an effective and less invasive way to fight melanoma (NASCIMENTO *et al*., 2019).

3.1.5. *Solanum torvum*

Solanum torvum, also known as Jurubeba in Brazil, is a plant found in South America, Africa and Asia, and is widely used in medicine around the world. This plant can be used as sedative and diuretic, and the leaves are used as haemostatic (LOGANAYAKI *et al*., 2010). Its chemical constituents have several uses in medicine, including alkaloids, flavonoids, saponins, tannins and glycosides (CHAH *et al*., 2000), as well as vitamins including B and C groups, and iron salts. This plant has great antioxidant power and can eliminate free radicals, preventing and intervening in many diseases (JAISWAL, 2012). Also, it shows anti-inflammatory (NDEBIA *et al*., 2006; BHAKUNI *et al*., 1969), antimicrobial (BALACHANDRAN *et al*., 2012; BARI *et al*., 2010; CHAH *et al*., 2000), antifungal (BARI *et al*., 2010), antiviral (ARTHAN *et al*., 2002) and anticarcinogenic effects (AL-HAY *et al*., 2018).

However, cases of poisoning by susumber berries (a member of the Solanacea fruit family) have been reported. There are several toxins in this family, including steroidal glycoalkaloids, but the specific poisoning toxin is unknown (ANTEZANA *et al*., 2012). Steroidal glycoalkaloids are present in numerous species of Solanum genus (family Solanaceae) and have reported toxicity in gastrointestinal tract such as abdominal pain, profuse vomiting, and neurological effects such as blurred vision, dysarthria, bilateral hand weakness, and unsteady gait (ANTEZANA *et al*., 2012; SMITH *et al*., 2008).

3.1.6. Antioxidant effect

S. torvum exhibited antioxidant activity against DPPH (2,2-diphenyl-1-picrylhydrazyl) stabilizing free-radical molecules, and hydrogen peroxide. DPPH scavenging activity was observed in their fruits and leaves. In fact, phenolics concentration found in many plants may be related to their antioxidant activities. Polyphenols are capable to donate hydrogen and have metal-chelating potential, another protection against iron and copper induced free radical reactions (RICE-EVANS *et al*., 1995). The phenolic content presented in the fruits is higher than that observed in the leaves. *S. torvum* also demonstrated ability to chelate Fe+2 ions, an important mechanism of antioxidant activity (LOGANAYAKI *et al*., 2010). The antioxidant activity of the isolated protein present in the aqueous extract *S. torvum* seeds was shown in an agarose gel electrophoresis, when the protective effect of the protein on hydrogen peroxide-mediated DNA damage was observed. This protein showed to be an efficient antioxidant, even at low doses, when compared to conventional synthetic antioxidants (SIVAPRIYA *et al*., 2007).

3.1.7. Anti-inflammatory effect

S. torvum is used in Cameroonian traditional medicine for pain and inflammation. Also, it can be employed for treatment of fever, wounds and tooth decay (JAISWAL, 2012), as well as for toothache by inhalation of the smoke from burnt seeds (BHAKUNI *et al*., 1969).

Aqueous extract of *S. torvum* leaves is responsible for analgesic and anti-inflammatory effects by inhibiting inflammatory mediators release, including prostaglandins, and COX enzyme. In an experiment using rats induced to pain and edema, *S. torvum* extract from leaves decreased the number of writhes similar to tramadol, while the analgesic effects were similar to those obtained with morphine and tramadol. Moreover, effects in reducing edema induced by carrageenan injection were satisfactory, based on the significant edema attenuation by *S. torvum* aqueous extract (NDEBIA *et al*., 2006). Therefore, the study, showed that oral administration of *S. torvum* extract can act by suppressing the later phase of the inflammation.

3.1.8. Antimicrobial and Antiviral activity

The methanolic extracts of *S. torvum* fruits and leaves, which contain active phytochemicals, such as alkaloids, flavonoids, saponins, tannins and glycosides showed a wide spectrum of antimicrobial activities in human clinical studies (Bari *et al*., 2010; CHAH *et al*., 2000). Important antimicrobial activity of the extract of *S. torvum* fruits against Actinomyces pyogenes, Bacillus subtilis,

Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, Streptococcus pyogenes, Aspergillus niger and Candida albicans was shown through disc diffusion method for the determination of the minimum inhibitory concentration (MIC) (CHAH *et al*., 2000). *S. torvum´*s root, even at low concentrations, also showed potential to inhibit the bacterial growth of Streptococcus-β-haemolyticus and Vasin factum using disc diffusion assay method (BARI *et al*., 2010).

Methyl caffeate, one of the components isolated from the fruits of *S. torvum* inhibited α-glucosidase activity, oxidative stress activity and showed anti-platelet and anti-proliferative activities (BALACHANDRAN *et al*., 2012). The analyses of methyl caffeate against M. tuberculosis exhibited prominent activity on mycobacterial strains, evaluated against standard sensitive strain M. tuberculosis H37Rv and rifampicin isolate M. tuberculosis. This compound showed a potent in vitro antiTB activity observed in MIC experiment (BALACHANDRAN *et al*., 2012).

Antiviral isoflavonoid sulfate and glycosides were also isolated from the fruits of *S. torvum* (LOGANAYAKI *et al*., 2010) The antiviral activity is observed against Herpes simplex virus type 1 (HSV-1) employing the colorimetric method. Isoflavonoid sulfate, named torvanol A, and steroidal glycoside, named torvoside H, together with torvoside A, isolated from a methanolic extract of *S. torvum* fruits exhibited antiviral activity, as judged by their IC50 values, using the reference compound Acyclovir (ARTHAN *et al*., 2002).

3.1.9. Anticancer activity

The *S. torvum* fruit contains many chemical components such as triacontane derivatives, chlorogenone and neochlorogenone, isoflavonoid sulfate and steroidal glycosides. Methyl caffeate also plays an important role on anticancer activity against MCF-7 (breast carcinoma), A549 (lung adenocarcinoma), COLO320 (colon carcinoma), HepG-2 (liver hepatocellular carcinoma) and Vero cells (Cercopithecus aethiops kidney). (BALACHANDRAN *et al*., 2015). The cytotoxic properties of methyl caffeate were better against MCF-7 cells than against A549, COLO320 and HepG-2 cells, owing to the significant reduction on cell proliferation, increased formation of fragmented DNA and apoptosis via caspase activation (BALACHANDRAN *et al*., 2015).

The ethanolic extract of the *S. torvum* fruits showed important cytotoxic activity against EAC (Ehrlich ascites carcinoma) cell lines. Their anticancer agents include alkaloids, flavonoids and phenolic compounds, showing that these components have important activity against esophageal cancer (SWAYAMSIDDHA *et al*., 2014).

Glycoalkaloids isolated from *S. torvum* callus revealed cytotoxic activity against breast and lymphoblastic leukemia cell lines, according to obtained IC50 values: 28.36 µg.mL-1 and 1.44 µg.mL-1 respectively. Total callus extract was more cytotoxic than isolated glycoalkaloids, illustrated by lower IC50 values of 2.22 µg.mL-1 in breast and 1.40 µg.mL-1 in lymphoblastic leukemia, suggesting a synergistic effect with other components (AL-HAY *et al*., 2018).

3.1.10. Antitumoral effects in Melanoma

S. torvum callus extract and isolated glycoalkaloids exhibited cytotoxic properties against melanoma. Data from previous study compared callus methanolic extract with pure glycoalkaloids, and showed that callus extract was more cytotoxic than isolated glycoalkaloids. The synergistic effect of phenolics and glycoalkaloids contained in the callus extract may be responsible for the greater cytotoxic activity of the extract. Flavonoids have been reported to modulate vascularization and cell proliferation, differentiation and apoptosis, thereby repressing various processes associated with cancer (AL-HAY *et al*., 2018). In addition, both callus extract and pure isolated glycoalkaloids were harmless on normal cells.

A compound detected on the callus extract named Solamargine, and also the glycoalkaloids, showed a fast and efficient inhibition of melanoma development via cell necrosis in vitro (AL-HAY *et al*., 2018).

According to Li *et al* (2014), steroidal glycosydes isolated from the *S. torvum* fruits showed cytotoxic activity against the human melanoma cell line A375. The methanolic extract of *S. torvum* fruits, obtained by chromatographic purification of 50% methanol

extract of *S. torvum* fruits on semi-preparative HPLC (High Performance Liquid Chromatography) showed moderate cytotoxic activity, which may be attributed to the steroidal glycosides that represent the main characteristic constituents of the *S. torvum* fruits.

Moreover, the antimelanogenesis effects of *S. torvum* were evaluated in mouse melanoma cell lines B16 (ARUNG *et al*., 2009) determined by using a tyrosinase enzyme inhibition assay, and a 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging assay. *S. torvum*'s root was found to be potent inhibitor of melanin formation without significant cytotoxicity.

3.1.11. *Lobelia inflata*

The *Lobelia inflata* is native from eastern North America. The Lobelia genus is a tribute to the botanist who described it, Mathias L´Obel. Lobelia species have long been used for the treatment of diseases, both in the form of infusions and tinctures (FOLQUITTO *et al*., 2019). Lobelia is monocarpic and can be arisen annual or biennial, in this case being resistant to frost (HUGHES *et al*., 2014). There is an interest in Lobelia alkaloids, mainly Lobeline, because of its activity in the central nervous system as a nicotinic receptor ligand and neurotransmitter transporter inhibitor, it is a candidate for treatment of methamphetamine abuse (KURSINSZKI; SZÖKE, 2015).

There are many isolated substances in the Lobelia genus, among them: flavonoids, terpenes and triterpenes, saponins and coumarins that probably have pharmacological effects (FOLQUITTO *et al*., 2019). This plant, which belongs to traditional Chinese medicine, has several applications related to anti-inflammatory (LIU *et al*., 2019), antioxidant and hepatoprotective effects (CUI *et al*., 2016), and anti-melanoma effects (IRENO *et al*., 2020), justifying the several ongoing studies with this plant.

L. inflata can be used in distinct manners, such as tincture, powder, syrup and infusion, drawing the attention of researchers due to its hypnotic, emetic, astringent and anti-asthmatic properties (FOLQUITTO *et al*., 2019). In addition, the methanolic extract of the Lobelia leaves

demonstrated antidepressant activity in mice (SUBARNAS *et al*., 1992).

The alkaloids present in the Lobelia plant have a number of properties: primary stimulant and secondary depressant of sympathetic and parasympathetic ganglia, the neuromuscular junction, the adrenal and carotid and aortic body chemoreceptors besides local anesthesticanesthetic properties (DWOSKIN, CROOKS, 2002). In a comparison between a group of animals that received carrageenan and was treated with Lobelia extract, with another group that only received inflammatory stimulus, the first group demonstrated a lower recruitment of leukocytes, mainly neutrophils (GARCIA *et al*., 2020).

In mice inoculated with melanoma B16-F10 cells, it was observed that the administration of the plant hydroalcoholic extract reduced the inflammatory activity, pro-inflammatory cytokines, melanoma growth and mortality of the tested mice (GARCIA *et al*., 2020; IRENO *et al*., 2020).

According to Harrod *et al*. (2004), Eyerman and Yamamoto (2005) in other studies of pharmacological activity in the mammalian brain it was demonstrated that the lobeline alkaloid extracted from *L. inflata* can inhibit behavioral effects of methamphetamine and can also be used in pharmacotherapy for abuse of psychostimulants including smoking cessation.

L. inflata can also be used as respiratory stimulant, since lobeline alkaloid stimulates the respiratory center through aortic and carotid chemoreceptors (MA; WINK, 2008).

However, the indiscriminate use of Lobelia, twice the recommended dose, may lead to side effects such as nausea, cough, vomiting, diarrhea, tremors and throat irritation (STANSBURY *et al*., 2013).

3.1.12. Anti-inflammatory effects

The organism undergoes changes in the face of external aggressions or invasion by microorganisms, which are represented by inflammation (TOWNSEND *et al*, 2019). The combined effects of cells and proteins, such as T cells and antibodies, produce an inflammatory response, being an efficient defense mechanism of the human body (LEVINSON, 2016). Inflammation has the purpose of eliminating the aggressor agents through the recruitment of host defense cells and molecules (KUMAR *et al*., 2016). On the other hand, inflammation can be associated with carcinogenesis, for example, prostaglandins are inflammatory factors, and chronic inflammation predisposes to carcinogenesis (DAI; MUNPER, 2010).

For a long time, plants have been used as a treatment for several diseases and nowadays many therapies are based on traditional medicine (MAIONE *et al*., 2015). The anti-inflammatory effects of products isolated from plants represent one of the most reported biological activities among the studies published so far (AZAB *et al*., 2016). *L. inflata* is a plant that is currently being studied and favorable results regarding its anti-inflammatory effects have been continuously shown.

It was observed that the hydroalcoholic extract of Lobelia affect the number of leukocytes circulating in the peritoneal cavity, in addition to suppressing cellular recruitment (IRENO *et al*., 2020).

3.1.13. Antitumor effects in Melanoma

The incidence rate of melanoma and associated risk behaviors continue to increase in the USA (GUY *et al*., 2015). In terms of increased incidence, no other solid or blood malignancy has increased so dramatically in recent years (MISHRA *et al*., 2018). The pathophysiology of skin cancer involves the reducing of apoptosis as well as the increasing of proliferation and survival of cells in the epidermis, as a failure of the immune system. The development of cancer is associated with environmental, chemical, physical, metabolic and genetic factors (DAI, 2010). The most prevalent environmental risk for the development of cutaneous melanoma is sun exposure in childhood and adulthood (AUTIER; DORÉ, 1998). Many clinical trials of vaccines and cytokines are underway, but there is no evidence of adjuvant postoperative therapy to increase patient survival (THOMPSON *et al*., 2005).

The survival prognosis of the patient with melanoma is associated with the thickness and invasion level of primary cutaneous melanoma (NASER, 2011). Due to resistance to chemotherapy drugs in late and recurrent stages of malignant melanoma, many patients seek for complementary and alternative drugs (LING *et al*., 2016). In Western countries, from 40% to more than 90% of all cancer patients use alternative medicine, being the decrease in side effects one of the reasons for this choice (LOQUAI *et al*., 2016). In Asian countries, for instance, for thousands of years traditional Chinese medicinal herbs have been used to treat various types of cancer (ZHANG *et al*., 2017).

Herbal medicines are widely used by people with cancer in association with chemotherapy due to their anti-cancer properties and supportive care (YAP *et al*., 2010). *L. inflata* was studied in 1885 because it is a source of alkaloid substances and was known for its therapeutic properties (IRENO *et al*., 2020). *L. inflata* is an alternative treatment for melanoma, proving to be effective when used in mice inoculated with melanoma. The site taken by the tumor is responsible for causing stress in the endoplasmic reticulum due to poor vascularization, few nutrients and acidic pH (SANO; REED, 2013). After administration of the plant hydroalcoholic extract in mice peritoneal cavity, there was a reduction in inflammatory cells, inflammatory cytokines (IL-1, IL-6 and TNF α) and local edema (GARCIA *et al*., 2020).

The development of cancer is characterized by angiogenesis. This process takes place so that the tumor is supplied with nutrients and oxygen necessary for its growth. The vessels formed in the tumors do not have their normal structure, are not hierarchically organized and have a greater permeability than normal vessels (ZANOTELLI; REINHART-KING, 2018). In 1971, when Folkman suggested an association between angiogenesis and tumor growth, an attempt was made to target angiogenesis for cancer treatment (LI *et al*., 2014). There is evidence of a large increase in vessel density during the transition from benign to malignant (POLLARD, 2008). Thus, in experimental model of mice treated with *L. inflata*, there was a positive impact on melanoma therapy, with reduction of the vessels number (IRENO *et al*.,2020).

Accordingly, *Lobelia inflata*, *Arctium lappa* and *Solanum torvum*, show promise as future alternatives in the treatment of melanoma, with regard to their antitumor and anti-inflammatory effects (Table 1), reinforcing the importance of continuing studies based on these plants. .

Table 1. Effects of *S. torvum*, *A. lappa* and *L. inflata*.

Plant	Anti-inflammatory effects	Anti-tumor effect	Effects on melanoma
S. torvum	Inhibition of inflammatory mediators (Prostaglandin, COX) and suppression of the later stage of inflammation. NDEBIA *et al.*, 2006	Oxidative stress inhibiting activity, anti-proliferative activity and cytotoxic properties against tumor cells. BALACHANDRAN *et al.*, 2015	Inhibition of melanoma by cell necrosis, cytotoxic performance, and melanin inhibition. ARUNG *et al.*, 2009 AL-HAY *et al.*, 2018 LI *et al.*, 2014
A. lappa	Inhibition of induced nitric oxide synthase (iNOS) expression and nitric oxide (NO) production. CHAN *et at.*, 2011	Down-regulation of protein cyclin D1 expression in a dose and time-dependent manner. MATSUZAKI *et al.* 2008	The compound Lappaol F inhibits the growth in tumor cell lines. SUN *et al.*, 2014
L. inflata	Reduces the number of white blood cells, improve the local hyperemia degree, TNF-α and IL-6 levels. LIU *et al.* 2018	Lobeline can moderately inhibit P-gp mediated efflux and reverse P-gp dependent resistance at non-toxic concentrations. MA; WINK, 2008	A positive impact on melanoma therapy, reducing the number of new vessels. IRENO *et al.*, 2020

4. CONCLUSION

The dynamic activities of medicinal plants and synthetic compounds can point out that medicinal plants, along with their effects and uses, have never been ignored. The active ingredients of medicinal plants including flavonoids and other phenolic compounds with antioxidant activity can scavenge free radicals and thus be effective against tumors.

Research lines that investigated the antitumor activities of *Arctium lappa* involve mainly studies using human cell lines. *A. lappa* extract has been shown to reduce cell viability, causing apoptosis and also reducing proliferation in different tumor cells. Pharmacological studies on *S. torvum* have focused on antioxidants and anticancer activities. *S. torvum* have been explored for anticancer activities and have exhibited significant results. Some studies showed that *L. inflata* reduced the recruitment of inflammatory cells and had a striking impact on tumor growth.

There are still many questions about the effects of medicinal plants for which we have limited information, and therefore deserve much further investigation. More clinical research involving trials and cohort human studies should be conducted to provide key evidence of the medical benefits of these plants.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest regarding the publication of this paper.

REFERENCES

Al-Hay, H Abd *et al*. Prospective Role of Solanum Cultures in Producing Bioactive Agents against Melanoma, Breast, Hematologic Carcinomas Cell Lines and Associated Microbiome. Journal of Biological Sciences, 18: 297-306, 2018. http://dx.doi.org/10.3923/jbs.2018.297.306.

Antezana, A.; *et al*. Susumber berries: Unexpected cause of cholinergic poisoning. Neurol Clin Pract. 2(4):362-363, 2012. doi:10.1212/CPJ.0b013e31826af1f6

Arthan, D.; Svasti, J.; Kittakoop, P.; Pittayakhachonwut, D.; Tanticharoen, M.; Thebtaranonth, Y. Antiviral isoflavonoid sulfate and steroidal glycosides from the fruits of *Solanum torvum*. Phytochemistry.59(4):459-63. Feb 2002. doi: 10.1016/s0031-9422(01)00417-4.

Arung E.T.; Kusuma I.W.; Christy E.O; Shimizu K.; Kondo R. Evaluation of medicinal plants from Central Kalimantan for antimelanogenesis. J Nat Med. 63(4):473-80, 2009. doi: 10.1007/s11418-009-0351-7.

Autier P; Doré J.F.; Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. Int J Cancer. 77(4):533-537, 1998. doi:10.1002/(sici)1097-0215(19980812)77:4<533::aid-ijc10>3.0.co;2-7

Awale, S.; *et al*. Identification of arctigenin as an antitumor agent having the Ability to Eliminate the Tolerance of Cancer Cells to Nutrient Starvation. Cancer Research, 66(3):1751-1757, 2006. http://dx.doi.org/10.1158/0008-5472.can-05-3143.

Azab, A.; Nassar, A;. Azab, A. N. Anti-Inflammatory Activity of Natural Products. Molecules. 21(10):1321, 2016. doi:10.3390/molecules21101321

Balachandran, C. *et al*. Antimicrobial and Antimycobacterial Activities of Methyl Caffeate Isolated from *Solanum torvum* Swartz. Fruit. Indian Journal of Microbiology. 52(4): 676-681, 2012. http://dx.doi.org/10.1007/s12088-012-0313-8.

Balachandran, C. *et al*. In vitro anticancer activity of methyl caffeate isolated from *Solanum torvum* Swartz. fruit. Chemico-Biological Interactions. 242: 81-90, 2015. http://dx.doi.org/10.1016/j.cbi.2015.09.023.

Bari, M.A., Islam W.; Khan A.R.; Mandal A. Antibacterial and antifungal activity of *Solanum torvum* (solanaceae). Int. J. Agric. Biol., 12: 386–390, 2010.

Bhakuni, D.S.; Dhar, M.L.; Dhawan, B.N.; Meirotra, B.N. Screening of Indian plants for biological activity. II. Indian J Exp Biol 7(4): 250-262, 1969.

Cassileth, B.R.; Barazzuol, J.D. Herbal products and other supplements: Problems of special relevance to surgery. Journal of Pelvic Surgery, v.7, 21-26, 2001.

Chah, K.F.; Muko K.N.; Oboegbulem S.I. Antimicrobial activity of methanolic extract of *Solanum torvum* fruit. Fitoterapia. 71(2):187-9, 2000. doi: 10.1016/s0367-326x(99)00139-2.

Chan, Y.S; Cheng, L.N.; Wu, J.H.; Chan, E.; Kwan, Y.W.; Lee S. M.; Leung, G.P.; Yu, P.H.; Chan, S.W. A review of the pharmacological effects of *Arctium lappa* (burdock). Inflammopharmacology. 19(5):245-54, 2011. doi: 10.1007/s10787-010-0062-4.

Cho, M.K.; Park, J.W.; Jang, Y.P.; Kim, Y.C.; Kim, S.G. Potent inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by dibenzylbutyrolactone lignans through inhibition of I-kappa B alpha phosphorylation and of p65 nuclear translocation in macrophages. Int Immunopharmacol. 2(1):105-16, 2002. doi: 10.1016/s1567-5769(01)00153-9.

Cui, X.; Gu, X.; Kang, W. Antioxidant activity in vitro and hepatoprotective effects in vivo of compound Lobelia. Afr J Tradit Complement Altern Med. 12;13(5):114-122, 2016. doi: 10.21010/ajtcam.v13i5.15. PMID: 28487901; PMCID: PMC5416629.

Dai, J.; Mumper, R.J. Plant Phenolics: Extraction, Analysis and Their Antioxidant and Anticancer Properties. Molecules, 15, 7313-7352, 2010.

Dwoskin, L.P;Crooks, P.A. A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. Biochem Pharmacol. 15;63(2):89-98, 2002. doi: 10.1016/s0006-2952(01)00899-1. PMID: 11841781.

Eyerman, D. J.; Yamamoto, B. K. Lobeline Attenuates Methamphetamine Induced Changes in Vesicular Monoamine Transporter 2 Immunoreactivity and Monoamine Depletions in the Striatum. The Journal of Pharmacology and Experimental Therapeutics. 312:160-169, 2005.

Ferracane, R.; Graziani, G; Gallo, M.; Fogliano, V.; Ritieni,

A. Metabolic profile of the bioactive compounds of burdock (*Arctium lappa*) seeds, roots and leaves. J Pharm Biomed Anal. 20;51(2):399-404, 2010. doi: 10.1016/j.jpba.2009.03.018.

Folkman, J. Role of Angiogenesis in Tumor Growth and Metastasis. Seminars in Oncology, Boston, 29 (6):15-18, 2002. http://dx.doi.org/10.1016/s0093-7754(02)70065-1.

Folquitto, D.G.; Swiech, J.N.D; Pereira, C.B. *et al*. Biological activity, phytochemistry and traditional uses of genus Lobelia (Campanulaceae): A systematic review. Fitoterapia. 134:23-38, 2019. doi:10.1016/j.fitote.2018.12.021

Garcia, N.P.; Ireno, L.C.; De Castro, M.P. *et al*. Antitumoral effect of *Lobelia inflata* in an experimental mouse model of melanoma. Biomed J Sci & Tech Res 25: 18856-18864, 2020.

Geiger, T.R.; Peeper, D. S. Metastasis Mechanisms. Biochimica Et Biophysica Acta (bba) - Reviews on Cancer, Amsterdam, 1796(2): 293-308, 2009. http://dx.doi.org/10.1016/j.bbcan.2009.07.006.

Gu, Y.; Qi, C.; Sun, X.; Ma, X.; Zhang, H.; Hu, L.; Yuan, J.; Yu, Q. Arctigenin preferentially induces tumor cell death under glucose deprivation by inhibiting cellular energy metabolism. Biochem Pharmacol.15;84(4):468-76, 201276, 2012. doi: 10.1016/j.bcp.2012.06.002.

Guy, G.P. Jr.; Thomas, C.C.; Thompson, T.; Watson, M.; Massetti, G.M.; Richardson, L.C; Centers for Disease Control and Prevention (CDC). Vital signs: melanoma incidence and mortality trends and projections - United States, 1982-2030. MMWR Morb Mortal Wkly Rep. 5;64(21):591-6, 2015.

Harrod, S. B.; Dwoskin, L. P.; Bardo, M. T. Lobeline produces conditioned taste avoidance in rats. Pharmacology Biochem Behav. 78:1-5, 2004.

He, Y.; Fan, Q.; Cai, T.; Huang, W.; Xie, X.; Wen, Y.; Shi Z. Molecular mechanisms of the action of Arctigenin in cancer. Biomed Pharmacother. 108:403-407, 2018. doi: 10.1016/j.biopha.2018.08.158.

Hirose, M.; Yamaguchi, T.; Lin, C.; Kimoto, N.; Futakuchi, M.; Kono, T.; Nishibe, S.; Shirai, T. Effects of arctiin on PhIP-induced mammary, colon and pancreatic carcinogenesis in female Sprague-Dawley rats and MeIQx-induced hepatocarcinogenesis in male F344 rats. Cancer Lett. 3;155(1):79-88, 2000. doi: 10.1016/s0304-3835(00)00411-0.

Hsieh, C.J; Kuo, P.L; Hsu, Y.C.; Huang, Y.F.; Tsai, E.M.; Hsu, Y.L. Arctigenin, a dietary phytoestrogen, induces apoptosis of estrogen receptor-negative breast cancer cells through the ROS/p38 MAPK pathway and epigenetic regulation. Free Radic Biol Med. 67:159-70, 201470, 2014. doi: 10.1016/j.freeradbiomed.2013.10.004.

Hughes, P.W.; Jaworski, A.F.; Davis, C.S.; Aitken, S.M.; Simons, A.M. Development of polymorphic microsatellite markers for Indian tobacco, *Lobelia inflata* (Campanulaceae)() (1.). Appl Plant Sc.2(4): 2014. doi:10.3732/apps.1300096

Ireno, LC.; Garcia, NP.; Moreira, MRA. *et al*. Evaluation of the *Lobelia inflata* extract in the histopathological profile of melanoma in experimental model. Biomed J Sci & Tech Res 26(3)-2020. doi: 10.26717/BJSTR.2020.26.004348

Iwakami, S., Wu, J.B.; Ebizuka, Y.; Sankawa, U. Platelet activating factor (PAF) antagonists contained in medicinal plants: lignans and sesquiterpenes. Chem Pharm Bull. 40(5):1196-8, 1992, doi: 10.1248/cpb.40.1196.

Jaiswal, B.S. *Solanum torvum*: A review of its traditional uses, phytochemistry and pharmacology. Int J Pharm Bio Sci. 3 (4):104-111, 2012.

Kala, C.P.; Dhyani, P.P.; Sajwan, B.S. Developing the medicinal plants sector in northern India: challenges and opportunities. J Ethnobiol Ethnomed. 2:32, 2006. doi:10.1186/1746-4269-2-32

Karlsson, A; Saleh, S. Checkpoint inhibitors for malignant melanoma: A Systematic Review and Meta-Analysis. Clinical, Cosmetic and Investigational Dermatology, [s.l.], 10: 325-339, 2017339, 2017. http://dx.doi.org/10.2147/ccid.s120877.

Kumar, V., Abbas, A.K., Fausto, N., Aster, J.C. Robbins & Cotran Patologia: Bases Patológicas das Doenças. Elsevier, Rio De Janeiro, 2016.

Kumari, P.; Luqman, S.; Meena, A. Application of the combinatorial approaches of medicinal and aromatic plants with nanotechnology and its impacts on healthcare. Daru. 27(1):475-489. 2019. doi:10.1007/s40199-019-00271-6

Kursinszki L, Szőke É. HPLC-ESI-MS/MS of brain neurotransmitter modulator lobeline and related piperidine alkaloids in *Lobelia inflata* L. J Mass Spectrom. 50(5):727-33, 2015. doi: 10.1002/jms.3581. PMID: 26259655.

Lee, S.; Shin, S.; Kim, H. *et al*. Anti-inflammatory function of arctiin by inhibiting COX-2 expression via NF-κB pathways. J Inflamm (Lond). 7;8(1):16. 2011. doi: 10.1186/1476-9255-8-16.

Levinson, W. Microbiologia médica e imunologia. Porto Alegre, AMGH, 2016.

Li, J; Zhang, L; Huang, C; Guo, F; Li, Y. Five new cyotoxic steroidal glycosides from the fruits of *Solanum torvum*. Fitoterapia. 93:209-215, 2014. http://dx.doi.org/10.1016/j.fitote.2014.01.009.

Ling, B.; Michel, D.; Sakharkar, M.K.; Yang, J. Evaluating the cytotoxic effects of the water extracts of four anticancer herbs against human malignant melanoma cells. Drug Des Devel Ther. 10:3563-3572, 2016. doi:10.2147/DDDT.S119214

Liu, B.; Bai, M.; Peng, M.; Miao, M. Anti-inflammatory effect and the effect on acute pharyngitis rats model of compound Lobelia oral liquid. Saudi J Biol Sci.;26(3):577-581, 2019. doi:10.1016/j.sjbs.2018.11.018

Loganayaki, N; Siddhuraju, P; Manian, S. Antioxidant activity of two traditional Indian vegetables: solanum nigrum l. and *Solanum torvum* l. Food Science and Biotechnology. 19(1): 121-127, 2010. http://dx.doi.org/10.1007/s10068-010-0017-y.

Loquai, C.; Dechent, D.; Garzarolli, M. *et al*. Risk of interactions between complementary and alternative medicine and medication for comorbidities in patients with melanoma. Med Oncol.;33(5):52. 2016. doi:10.1007/s12032-016-0764-6

Lu, S.; Zhu, Q.; Zhang, Y.; Song, W.; Wilson, M.J.; Liu, P. Dual-Functions of miR-373 and miR-520c by Differently Regulating the Activities of MMP2 and MMP9. J Cell Physiol. 230(8):1862-70, 2015. doi: 10.1002/jcp.24914.

Ma Y.; Wink, M. Lobeline, a piperidine alkaloid from Lobelia can reverse P-gp dependent multidrug resistance in tumor cells. Phytomedicine. 15(9):754-758, 2008. doi:10.1016/j.phymed.2007.11.028

Maione, F.; Russo, R.; Khan, H.; Mascolo, N. Medicinal plants with anti-inflammatory activities. Nat Prod Res;30(12):1343-1352, 2016. doi:10.1080/14786419.2015.1062761

Matsuzaki, Y.; Koyama, M.; Hitomi, T.; Yokota, T.; Kawanaka, M.; Nishikawa, A.; Germain, D.; Sakai T. Arctiin induces cell growth inhibition through the down-regulation of cyclin D1 expression. Oncol Rep. 19(3):721-7, 2008.

Mishra, H.; Mishra, P.K;. Ekielski, A.; Jaggi, M.; Iqbal, Z.; Talegaonkar, S. Melanoma treatment: from conventional to nanotechnology. J Cancer Res Clin Oncol. 144(12):2283-

2302, 2018. doi: 10.1007/s00432-018-2726-1.

Moritani, S.; Nomura, M.; Takeda, Y.; Miyamoto, K. Cytotoxic components of Bardanaefructus (goboshi). Biol Pharm Bull. 19(11):1515-7, 1996. doi: 10.1248/bpb.19.1515.

Nascimento, B. A. C.; Gardinassi, L.G, Silveira, I.M.G.; Gallucci, M.G; Tomé, M.A. Oliveira, J.F.D, Moreira, M.R.A, Meirelles, A.F.G.; Faccioli, L.H, Tefé-Silva, C.; Zoccal; K. F. *Arctium lappa* Extract Suppresses Inflammation and Inhibits Melanoma Progression. Medicines (Basel). 29;6(3):81, 2019. doi: 10.3390/medicines6030081.

Naser, N. Cutaneous melanoma: a 30-year-long epidemiological study conducted in a city in southern Brazil, from 1980-2009. An Bras Dermatol.86(5):932-941, 2011. doi:10.1590/s0365-05962011000500011

Ndebia, E.J.; Kamgang, R.; Nkeh-ChungagAnye, B.N. Analgesic and anti-inflammatory properties of aqueous extract from leaves of *Solanum torvum* (Solanaceae). Afr J Tradit Complement Altern Med. 13;4(2):240-4, 2006. doi: 10.4314/ajtcam.v4i2.31214.

Pereira, J.V.; Bergamo, D.C.; Pereira, J.O.; França, S. C.; Pietro, R.C.; Silva-Sousa, Y.T. Antimicrobial activity of *Arctium lappa* constituents against microorganisms commonly found in endodontic infections. Braz Dent J. 16(3):192-6. 2005. doi: 10.1590/s0103-64402005000300004.

Pollard, J.W. Macrophages define the invasive microenvironment in breast cancer. J Leukoc Biol. 84(3):623-630, 2008. doi:10.1189/jlb.1107762

Rice-Evans, C.A, Miller, N.J, Bolwell, P.G, Bramley, P.M.; Pridham, J.B. The relative antioxidant activities of plant-derivedpolyphenolicflavonoids.FreeRadicRes.;22(4):375-83, 1995. doi: 10.3109/10715769509145649. PMID: 7633567.

Rodriguez, P., Blanco, J., Juste, S., Garces, M., Perez, R., Alonso, L., *et al*. Allergic contact-dermatitis due to burdock (Arctium-Lappa). Contact Dermat. 33, 134–135, 1995. doi: 10.1111/j.1600-0536.1995.tb00524.x

Rosko, A.J.; Vankoevering, K.K.; McLean, S.A.; Johnson, .TM.; Moyer, J.S. Contemporary Management of Early-Stage Melanoma: A Systematic Review. JAMA Facial Plast Surg. 1;19(3):232-238, 2017. doi: 10.1001/jamafacial.2016.1846.

Sano, R.; Reed, J.C. ER stress-induced cell death mechanisms. Biochim Biophys Acta.;1833(12):3460-3470, 2013. doi:10.1016/j.bbamcr.2013.06.028

Sen, S.; Chakraborty, R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: Importance, challenges and future. J Tradit Complement Med. 7(2):234-244. 2016. doi:10.1016/j.jtcme.2016.05.006

Sherr, C.J. Mammalian G1 cyclins. Cell. 18;73(6):1059-65, 1993. doi: 10.1016/0092-8674(93)90636-5.

Silveira, P. F.; Bandeira, M.A. M.; Arrais, P.S.D. Farmacovigilância e reações adversas às plantas medicinais e fitoterápicos: uma realidade. Revista Brasileira de Farmacognosia. 2008, 18(4), 618-626. https://doi.org/10.1590/S0102-695X2008000400021

Shinohara, K.; *et al*. Antimutagenicity Of Dialyzates of Vegetables and Fruits. Agricultural and Biological Chemistry, 52 (6): 1369-1375, 1988. http://dx.doi.org/10.1271/bbb1961.52.1369.

Sivapriya, M; Leela, S. Isolation and purification of a novel antioxidante protein from the water extract of Sundakai (*Solanum torvum*) seeds. Food Chemistry. 104(2) 510-517, 2007. http://dx.doi.org/10.1016/j.foodchem.2006.11.060.

Smith, S.W.; *et al*. Solanaceous steroidal glycoalkaloids and poisoning by *Solanum torvum*, the normally edible susumber berry. Toxicon. 52(6):667-76, 2008. doi:10.1016/j.toxicon.2008.07.016

Stansbury, J., Saunders, P. R., & Zampieron, E. The use of lobelia in the treatment of asthma and respiratory illness. Journal of Restorative Medicine, 2(1), 94-100, 2013.

Subarnas, A.; Oshima, Y.; Sidik, Ohizumi, Y. An antidepressant principle of *Lobelia inflata* L. (Campanulaceae). J Pharm Sci.81(7):620-621. 1992. doi:10.1002/jps.2600810705

Sun, Q.; Liu, K.; Shen, X.; Jin, W.; Jiang.; Sheikh, M.S, Hu, Y.; Huang, Y. Lappaol F, a novel anticancer agent isolated from plant *Arctium lappa* L. Mol Cancer Ther. 13(1):49-59, 2014. doi: 10.1158/1535-7163.MCT-13-0552.

Swayamsiddha, P.; Meenakshi, S. M; Ravichandran, N; Brindha, P. Anticancer activity of ethanolic extract of *Solanum torvum* sw. International Journal of Pharmacy and Pharmaceutical Sciences. 6:93, 2014.

Tamayo, C.; Richardson, M.A.; Diamond, S.; Skoda, I. The chemistry and biological activity of herbs used in Flor-Essence herbal tonic and Essiac. Phytother Res. 14(1):1-14, 200014, 2000. doi: 10.1002/(sici)1099-1573(200002)14:1<1::aid-ptr580>3.0.co;2-o.

Thompson, J.F.; Scolyer, R.A.; Kefford, R.F. Cutaneous melanoma. The Lancet, 365: 687-701, 2005.

Townsend, C. M.; Evers, B. M.; Beauchamp, R. D. & Mattox, K. L. - Sabiston Textbook of Surgery. The Biological Basis of Modern Surgical Practice. 18th Ed, Saunders Elsevier, 2019.

Urazova, L.N.; Kuznetsova, T.I.; Boev, R.S.; Burkova, V.N. Efficacy of natural L-asparagine in the complex therapy for malignant tumors in experimental studies. Exp Oncol. 33(2):90-3, 2011.

Vervoort, S.J.; Lourenço, A.R.; van Boxtel, R.; Coffer, P.J. SOX4 mediates TGF-β-induced expression of mesenchymal markers during mammary cell epithelial to mesenchymal transition. PLoS One. 8(1):e53238, 2013. doi: 10.1371/journal.pone.0053238.

Wu, J.G.; Wu, J.Z.; Sun, L.N; Han, T.; Du. J.; Ye, Q.; Zhang, H.; Zhang, Y.G. Ameliorative effects of arctiin from *Arctium lappa* on experimental glomerulonephritis in rats. Phytomedicine. 16(11):1033-41, 2009 doi: 10.1016/j.phymed.2009.04.005.

Yap, K.Y.; See, C.S.; Chan, A. Clinically- relevant chemotherapy interactions with complementary and alternative medicines in patients with cancer. Recent patents on food, nutrition & agriculture. 2:12-55, 2010.

Yari, S.; Karamian, R.; Asadbegy, M.; Hoseini, E.; Moazzami Farida, S.H. The protective effects of *Arctium lappa* L. Extract on testicular injuries induced by ethanol in rats. Andrologia. 50(9):e13086, 2018. doi: 10.1111/and.13086.

Zanotelli.; M.R.; Reinhart-King, CA. Mechanical Forces in Tumor Angiogenesis. Adv Exp Med Biol.1092:91-112. 2018. doi:10.1007/978-3-319-95294-9_6

Zhang, L.; Khoo CS.; Koyyalamudi, SR.; De Pedro, N.; Reddy, N. Antioxidant, anti-inflammatory and anticancer activities of ethanol soluble organics from water extracts of selected medicinal herbs and their relation with flavonoid and phenolic contents. Pharmacologia, 8:59-72, 2017.

Zhou, B.; Weng, G.; Huang, Z.; Liu, T.; Dai, F. Arctiin Prevents LPS-Induced Acute Lung Injury via Inhibition of PI3K/AKT Signaling Pathway in Mice. Inflammation. 41(6):2129-2135, 2018. doi: 10.1007/s10753-018-0856-x.