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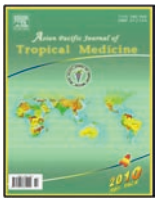

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Therapeutic and biological activities of *Calotropis procera* (Ait.) R. Br.

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ABSTRACT

Medicinal plants have been used to treat various ailments of the poor population around the world; hence the interest among researchers to know the active ingredients of certain plants has being increased. The *Calotropis procera (C. procera)* is a plant original from Africa, commonly found in northeastern Brazil. It is well known for their pharmacological properties, since it produces large amounts of latex. The important role that medicinal plants play in folk medicine has led us to develop this article in order to review the major pharmacological activities of *C. procera*.

1. Introduction

1.1. History

The search for new compounds that may be useful as a source of medicine has aroused the interest among many researchers who study plants and biologically active compounds, especially plants that are used by people since ancient times and are perpetuated in different cultures.

Calotropis procera (C. procera) (Ait.) R. Br, a plant of *Asclepiadaceae* family, is original from Africa, India and Persia, and is known popularly as jealousy, jealousy cotton, silk, flower-silk, milk or queimadeira. The scientific name of the family is derived from Asklepios, the Greek god of medicine[1].

This medicinal plant has stood out among the species adapted to the semi-arid northeastern Brazil. Its perennial, shrub or subarborea, can reach 3 feet tall. Its branches, leaves, stems and fruits are covered by serous, with strong presence of white latex, which flows in abundance when the tissue is broken[2,3].

C. procera is a typical plant of Asia and was brought to Brazil as an ornamental plant[4], which soon spread to the northeast of Brazil, using wind as main disseminator of its seeds. The climatic conditions in northeast Brazil have welcomed the development of this plant. Sometimes it is classified as an invasive plant, as they are able to establish themselves in the most unlikely places, under unfavorable conditions, invading unoccupied niches. Now, this plant belongs to a huge range of plants that can be used in folk medicine.

Different parts of the plant are used in the treatment of various diseases in folk medicine, and their effects were

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confirmed by scientific experiments. Reports of allergenic, analgesic, anti-inflammatory and anti-tumor activities were proven scientifically by assessment of molecules which were possibly involved in these activities. With increasing number of published articles involving the properties of this plant, we felt the need to prepare this review.

1.2. The latex of C. procera

C. procera is a plant well known for its ability to produce large quantities of latex[5,6], which is a milky liquid consisting of several biologically active compounds, including proteins, amino acids, carbohydrates, lipids, vitamins, alkaloids, carbonates, resins, tannins and terpenes[4].

When the plant is affected by any mechanical damage, their tissues are broken and secrete the latex, which, in contact with air, undergoes a coagulation process and results in the formation of rubber. The characterization of *C. procera* latex reinforces the idea that its production is involved in mechanisms of plant defense against attack by microorganisms such as viruses, fungi and insects. This natural secretion has an adhesive feature, allowing it to immobilize insects[7].

The presence of flavonoid glycosides and organic carbonates[8] extracted from the leaves of *C. procera* has been reported. Other chemicals such as alkaloids, anthocyanins, proteolytic enzymes, cardenolides, cardioactive glycosides and triterpenoids were also identified. Besides, the aforementioned flavonoids, flavonoids quercetin, resins, saponins and tannins were found too[9]. The latex can be obtained through a simple procedure based on centrifugation and dialysis. Its main constituent is rubber, which is highly insoluble in water[10].

The latex of *C. procera* contains several alkaloids (such as calotropin, catotoxin, calcilin, gigantin *etc*.) which are caustic and considered poisonous in nature[11] . Basak *et al*[12]. reported 29 cases of patients who presented with accidental ocular contact or injury with the latex of *C. procera*. All patients presented with sudden painless vision with photophobia. All eyes had conjuctival congestions and mild to severe corned edema with descemet's folds. However, the significant ocular morbidity caused by *C. procera* latex may be preventable by simple health education.

1.3. Ethnopharmacological study

The ethnopharmacologic approach is to associate information acquired from users of medicinal plants (traditional communities and experts) with chemical and pharmacological studies, which allows the formulation of hypotheses on the pharmacological activity (ies) and active substance(s) responsible for the reported therapeutic actions[13].

Many studies demonstrated biological activities of *C. procera*[5,14]. There are reports of inflammatory responses[15], analgesic, anti-microbial larvicides, nematicides, anticancer and weak antipyretic activities[16-22]. There are also studies of contraceptive activities reported in rats[23]. Because of these reports described in the literature and hypotheses about the useof *C. procera* latex as a powerful agent in the treatment of diseases, this plant stands out now in ethnopharmacology as a major source of compounds that can be used in the future as new drugs.

2. Methodology

This study performed a review about *C. procera*, plant of subspontaneous and common occurrence in the northeastern region of Brazil that stands out not only for its availability, but also for the use of its leaves, roots and stem by local population. Reports of this species have been described in articles published in many countries such as India, Japan, Persia, and confirmed its different therapeutic effects that benefit local population.

As source and search strategy, we searched electronic databases of Cochrane Library, LILACS and MEDLINE (MeSH). The search was performed using keywords like *C. procera*, latex, pharmacological, herbal and biochemical aspects, and toxicological effects with Boolean operators (and, or). We chose articles published from 1979 to 2009, all available online.

3. Biological properties of *C. procera* latex

The latex of *C. procera* is well known for its medicinal and toxic properties. When administered locally, it induces an intense inflammatory process that can be characterized by increased vascular permeability, edema and increased cellular infiltration[24]. This inflammation produced by latex involves the release of histamine from mast cells, and the presence of histamine in the latex itself. Thus, it appears that antihistamine drugs can be effectively used in the treatment of inflammation induced by the latex of this plant[25].

The inflammation produced by *C. procera* latex has been demonstrated in different experimental models of inflammation such as paw edema, air bag[26] and pleurisy in rats[25]. Thus, the latex is a potent phlogistic agent useful for evaluation of new anti-inflammatory drugs.

The effects promoted by inflammatory protein in the untreated latex can be effectively inhibited by cyproheptadine (CPH), while associated with inflammatory hyperalgesia, edema can be inhibited equally with both drugs, cyproheptadine (CPH) and rofecoxib[27].

About the anti-inflammatory effects of latex, it was observed that oral administration of aqueous and methanolic extracts of *C. procera* latex was able to significantly inhibit the formation of paw edema induced by carrageenin and formalin. Histological analysis has also shown that the extract of latex was more potent than phenylbutazone in inhibiting cellular infiltration and subcutaneous edema induced by carrageenan, suggesting that the extract of latex exercised its anti-inflammatory effect mainly by inhibiting histamine and bradykinin[28].

The latex of *C. procera* inhibited inflammation in models of paw edema and air bag in an experiment conducted with rats [16]. Treatment with the methanolic extract of *C. procera* produces an inhibition of joint inflammation, probably by its ability to reduce the cellular influx and vascular permeability. These results suggest that the latex has antiarthritic activity[29] .

Intraperitoneal injection of water-soluble *C. procera* (CPE) extract in mice induced migration of macrophages to the intraperitoneal cavity, confirming the proinflammatory effects of water-soluble *C. procera* extract. The direct effects of CPE on macrophages were then assessed by measuring the production of nitric oxide (NO) as an indicator for macrophage activation. Addition of CPE (1-10 lg/mL) to the culture medium of the murine monocyte/macrophage cell line RAW264.7 caused an increase in NO production in a time and dose-dependent manner. CPE-elicited NO production was blocked by application of an inhibitor of inducible nitric oxide synthase (iNOS). Expression of iNOS mRNA was induced by treatment of cultured macrophages with CPE. Injection of CPE in mice also resulted in an increase in plasma NO level. The results suggest that CPE activates macrophages and facilitates NO production via up-regulation of iNOS gene expression[30].

Other studies have shown that the protein fraction of *C. procera* latex produced a marked reduction in the number of rolling and adherent leukocytes in the mesenteric microvasculature as revealed by intravital microscopy. Its effects are mediated through elevation of serum levels of NO in the peritonitis model in rats[6].

The proteins in latex of *C. procera*, when in contact with the skin of persons, may trigger an allergic response and are imprisoned during the coagulation of latex[5]. Some proteins of this latex show a basic Isoplectric Point(IP) and have molecular weight(MW) ranging from 5 to 95 kDa. In the meantime, the most commonly found protein presents PM 26 KDa. In this pool of protein, cysteine proteinases, chitinases and anti-oxidant proteins (superoxide dismutase) are also found among others[31]. Tests using resolubilized protein of coagulated latex and untreated latex were able to stimulate immune activity when administered subcutaneously, developing cutaneous anaphylaxis and allergy[10].

More recent studies have demonstrated that latex proteins of *C. procera* can cause allergy subcutaneously. The Non Dialyzed Latex (NDL) fraction of this plant revealed antiinflammatory and analgesic effects intraperitoneally. This could be relevant in determining whether the NDL fraction could induce such activity when analyzed by oral path[5] .

The latex of the medicinal plant *C. procera* has anti-inflammatory and antinociceptive activity. The antitumor activity tested in trials using different tumor cell lines showed it was able to inhibit the development of cell lines HL-60 (leukemia), HCT-8 (colon cancer), MDA-MB-435 (breast cancer) and F295 (cell cancer of the brain) when analyzed by MIT testing[15] .

The *in vitro* cytotoxic activity of protein laticifer (LP), recovered from the latex of *C. procera*, was evaluated. LP exhibited considerable cytotoxicity IC (50), with values ranging from 0.42-1.36 μg/mL for cell lines SF295 and MDA-MB-435, respectively. When healthy mononuclear cells in peripheral blood were exposed to LP (10 g/mL) for 72 hours, no noticeable effects on the viability or morphology was observed[15] .

Studies with root methanolic extract, hexane extract, ethylacetate extract and aqueous extract of *C. procera* at various doses of 1, 5, 10 and 25 microg/mL in culture HEP2 cells revealed that the first three possessed cytotoxicity, whereas aqueous extract did not have cytotoxic effect. These results indicated that the root of *C. procera* inhibit the proliferation of Hep2 cell via apoptotic and the root extracts initiated apoptosis of Hep2 cells through cell cycle arrest at S phase, thus preventing cells from entering G2/M[32] .

UNBS1450 is a semi-synthetic derivative of 2-oxovoruscharin of *C. procera* that has been proven to be a potent sodium pump inhibitor, showing anti-proliferative and cell death-inducing activites. This anti-cancer potential of UNBS1450 01 is achieved by disorganization of the actin cytoskeleton after binding to the sodium pump at the cellular membrane, by inducing autophagy-related cell death, by repressing NF-kB activation as well as by down-regulating c-Myc in cancer cells[33-35] .

On the analgesic activity of *C. procera*, latex powder administered orally significantly reduced the writhing induced by acetic acid. This effect was more pronounced when compared to pre-treatment with aspirin[18] .

Nociceptive activity of latex protein has been reported using different pharmacological tests in mice, such as contortions induced by acetic acid, formalin test and hot plate. The nociceptive activity of this plant justifies its use in folk medicine, as the results showed that the analgesic properties appear to be independent of the opioid system[14] .

Research carried out with the chloroform fraction of *C. procera* root showed that this structure has potent anti-inflammatory activity against the exudative and proliferative phases of inflammation, and presents potential analgesic properties through tests assessing changes induced by acetic acid in rats[22] .

Research has shown that the spasmogenic and carminative properties of this plant is due to the ability to contract smooth muscles of the gastrointestinal tract .

Powder of *C. procera* latex decreased the frequency of diarrhea induced by castor oil, indicating a possible antidiarrhoeal activity similar to other drugs such as atropine and NSAIDs[36].

The liver is an organ of vital importance for the metabolism of exogenous substances such as drugs, viral infections and chronic alcoholism. Thus, if the natural defense mechanisms are not efficient in the elimination of these metabolites, the liver cells may be injured[37]. However, the latex of *C. procera* possesses potent antioxidant and hepatoprotective activities in the model of hepatotoxicity induced by carbon tetrachloride (CCl_4) in rats. Histological analysis of rat liver revealed necro-inflammatory changes associated with increased levels of thiobarbituric acid (TBARS), dinoprostone (PGE2), catalase and decreased levels of glutathione (GSH), superoxide dismutase (SOD) and glutathione peroxidase (GPx). The anti-inflammatory and

antioxidant effects of latex and silimarin were comparable, suggesting that the latex can be used as a hepatoprotective agent[38] .

The hepatoprotective effect *C. procera* extract was observed in rats with acetaminophen-induced hepatotoxicity. The use of alcoholic extract significantly reduced levels of liver enzymes ALT, AST, alkaline phosphatase and bilirubin[37].

The mosquito *Aedes aegypti* Linn is the vehicle of transmission of endemic diseases such as yellow fever and dengue. It is found in Africa, Latin America and especially in the northeast of Brazil, increasing the statistics of morbidity[10]. A study conducted in the 80s showed that the latex of *C. procera* has larvicidal activity[20].

The latex of *C. procera* appears to be toxic on the hatching of eggs and larvae of *Aedes aegypti*. This property increases the possibility of developing a formula that can be used in the Program for Prevention and Control of the proliferation of this insect, as well as other mosquitoes involved in transmission of disease to humans and animals[10].

Alzheimer's disease (AD) commonly known as dementia is an organic, progressive, chronic brain disorder characterized by multiple cortical functions, including memory, orientation, comprehension and language ability and learning. Currently, AD has no cure, but alternative pharmacological treatments can reduce the symptoms of cognitive failure and cause a slower progression of the disease[39] . Studies suggest that the latex of *C. procera* can be used to treat the early symptoms of dementia of Alzheimer type. Powder latex *C. procera* caused a decrease in the deposition of beta-amyloid in mouse brain, reporting a protector and antioxidant activity in this organ[39] .

The properties of *C. procera* go beyond the pharmacological effects. The ingestion of cut and dry leaves of *C. procera* by adult male goats at concentrations of up to 60% in the diet for 40 consecutive days did not produce changes clinically or in serum enzyme levels[40] indicating this plant can be used to supplement the diet during the great droughts, making 16.7% of the total feed offered to animals in confinement, not compromising the texture and taste of meat[41] .

The *in vitro* spasmolytic effect of aqueous extract of *C. procera* was evaluated using the smooth trachea muscle of pigs. The extract was used at concentrations of 50, 100 and 200 μg/mL, which all exhibited dose-dependent relaxing activity on smooth muscle[42].

Contraceptive effects were found in ethanol and aqueous extracts of the root of *C. procera*, which was able to interfere with the estrous cycle and inhibits ovulation in albino rats[23]. Strong antiinplante (inhibition 100%) and uterotropic activities were observed at the dose of 250 mg/kg (1/4 of the LD_{50}). No antiestrogen activity was detected. New work may elucidate the anti-estrogenic effect of extracts and isolate the main component responsible for such activity[43].

Studies on the dry latex of *C. procera*, administered at doses of 100 and 400 mg/kg, produce a dose-dependent decrease in the blood glucose and increase in the hepatic glycogen content. In addition, dry latex also produced the increase in the hepatic levels of the endogenous antioxidants, superoxide dismutase (SOD), catalase and glutathione in allon-induced diabetic in rats[44].

3. Conclucion

The results obtained in this work show the diversity of medicinal effects of *C. procera*. The broad pharmacological profile shown by this plant should be operated by the pharmaceutical industry for the development of new drugs, so the therapeutic arsenal for many diseases could be extended to benefit humanity.

Conflict of interest statement

We declare that we have no conflict of interest.

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