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PHARMACOLOGICAL EFFECTS OF *BAUHINIA FORFICATA* LINK

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ABSTRACT

Bauhinia forficata (BF) is widely used by the Brazilian population to treat different diseases. The scientific evidences of the hypoglycemic activity of this plant, led to a growing interest about the pharmacological properties resulted by the presence of bioactive compounds present in the leaves, flowers, stems, roots, and seeds. This study intended to carry out a bibliographic survey highlighting the main pharmacological activities of BF. Databases such as Scielo, PubMed and Lilacs were used, with the descriptors "Pharmacological activities of BF" and "Chemical constituents of BF." Using as inclusion criteria review articles and experimental studies employing in vitro and in vivo model studies published in the last five years. The results obtained demonstrate that BF possesses hypoglycemic, anti-oxidant, diuretic, anticoagulant, anti-inflammatory, anti-edema, antimicrobial, antiulcerogenic, antitumor, and anti-Alzheimer activity. The antioxidant property of BF can be explained by the presence of phenolic compounds such as gallic acid and flavonoids. The antitumor action is due to the presence of lectins, which are glycoproteins mainly arranged in-stock fabrics such as seeds of their fruits, being the other activities produced by the presence of free and glycosylated flavonoids. It is concluded that BF represents a plant resource of great importance for the development of new medicines and nutritional products in the area of Ethnopharmacology. However, it is considered that more studies regarding the toxicity of this plant should be performed to establish the effectiveness and safety of its use.

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INTRODUCTION

Bauhinia forficata (BF) Link belongs to the family Fabaceae and is native to Brazil, primarily concentrated in the regions of Rio de Janeiro to the Rio Grande do Sul, and is also geographically distributed in other countries such as Argentina, Paraguay, Uruguay, and Bolivia (Cechinel-Zanchett *et al*., 2019a; Santos, Fortunato, Spotorno, 2019). Popularly known as *cow's* paw", is a native plant from South America., due to the bilobed aspect of its leaves, it is one of the most studied species in reason to its therapeutic potential, which since 2009 is listed as a plant of medicinal interest, together with *Bauhinia variegata* and *Bauhinia affinis* in the National List of Medicinal Plants of National Interest (Caffaro, 2015). Phytochemical studies show known phytochemicals of the species, such as flavonoids, terpenes (Isofitol, α-humulene, β-pinene, β-ocimene, α-pinene, β-caryophyllene bicyclic germacrene) and phenolic compounds such as gallic acid. The hypoglycemic and antidiabetic effect is due to the quercetin and canpherolic compounds that have structural characteristics that favor the inhibitory effect on alpha-glycosidase, an enzyme responsible for catalyzing the final process in the digestion of carbohydrates. Other compounds were identified in this plant such as oxidosqualene cyclases (Srisawat *et al*, 2019; Marques *et al*., 2013). Numerous papers have been

published involving *in vivo* and *in vitro* assays demonstrating the hypoglycemic and antidiabetic effects of BF, as well as other pharmacological effects with equally quantitative and qualitative importance (Córdova *et al*., 2019; Souza *et al*., 2018; Pontes, 2017). Other pharmacological properties such as the antioxidant effect of BF can be demonstrated in experimental studies, where partial impairment of lipid peroxidation by Fe^{2+}, corresponding to the presence of gallic acid and quercetin compounds havebeen reported. The antioxidant effects are also reported by increasing glutathione concentration with aqueous extract insertion in the diet of pregnant diabetic rats (Pinafo *et al*, 2019; Ecker *et al*., 2015). Figure 1 summarizes the pharmacological properties of BF.

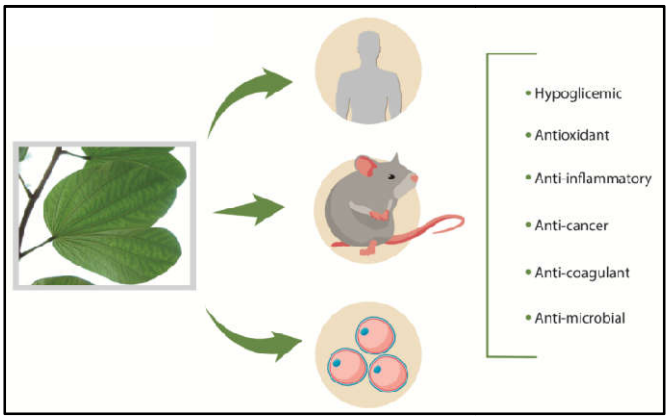

Figure 1. Pharmacological activities of *Bauhinia forficate* in humans, animal models and *in vitro* studies

With the exception for the inhibitory effect on cancer cells, the antibacterial action against strains of gram-positive bacteria, diuretic, anticoagulant, and antimitogenic effect are also pharmacological properties known due to the presence of flavonoids (Cechinel-Zanchett *et al*, 2019b; da Silva Pinto *et al*, 2019). This study aimed to perform a bibliographic review highlighting the main pharmacological activities of BF.

MATERIALS AND METHODS

Databases such as PubMed, Scielo, and Lilacs were used, with the descriptors "Pharmacological activities of *BF*" and "Chemical constituents of *BF*." Using as inclusion criteria review articles and experimental studies employing *in vitro* and *in vivo* model studies published in the last five years.

RESULTS AND DISCUSSION

The sections below raise the phytochemical composition of BF and its associations with human health.

Phytochemical composition of *Bauhinia forficata*

As *BF* is a plant popularly known in Brazil's traditional medicine to treat cardiovascular conditions but once it shows a plethora of bioactive compounds, there are many pathological conditions that could benefit with the use of this plant. Spectrophotometric analysis for the identification of phytochemical constituents of *BF* resulted in the identification of six flavonoids. Kaempferol-3,7-O-α-L-raminopyranoside was obtained from the flowers, and the others were found in the leaves: kaempferol, kaempferol 3,7-di-o-α-L-rhamnoside (canferitrine), quercetin 3,7-di-α-L-rhamnopyranoside, canferol 3-O- [β-D-glucopyranoside- (1-6) -α-L-rhamnopyranoside] -7-O-α-L-rhamnopyranoside and quercetin 3-O- [β-D-glucopyranoside- (1-6) -α-L-rhamnopyranoside] 7-O-α- Rhamnopyranoside (Pontes,2017). In addition to these free and glycosylated flavonoids in the form of quercetin and quercetin compounds, *BF* contains terpenes (Isofitol, α-humulene, β-pinene, β-ocimene, α-pinene, β-cariofilene bicycle germacrene), presence of alkaloids, mucilages, essential oils, tannins, cyanogenic and saponinheterosides (Marques *et al*.,2013; Souza *et al*., 2017; Batista *et al*., 2013). Srisawat *et al*. (2019) studied profile of triterpenoid aglycones of BF and identified four oxido-squalenecyclases that cyclases that are related to the diversity of triterpenols present in BF. This study also showed that this species highly accumulates α-amyrin. Some compounds from BF are found in Figure 2.

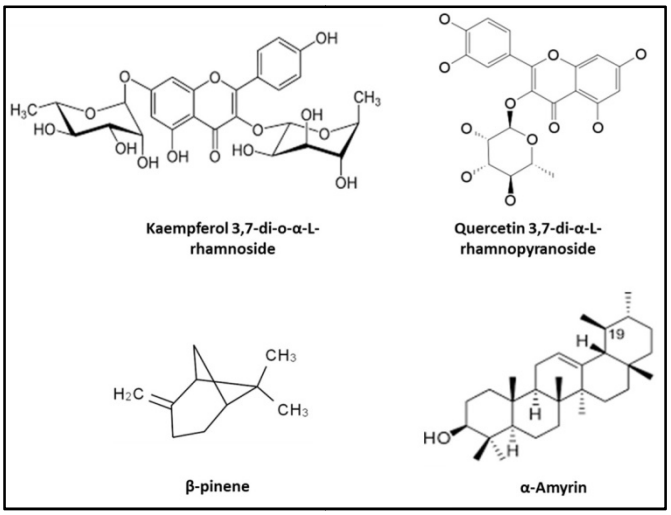

Figure 2. Structure of some phytochemicals found in *Bauhinia forficate*

Hypoglycemic activity

According to the studies of Santos, Fortunato, Spotorno (2019) and Silva and López (2015), the hypoglycemic property of *BF* corresponds to the presence of quercetin and kaempferol derivatives such as quercetin-3,7-di-o-α-L-rhamnopyranoside and Kaempferol3, 7-di-α-L-rhamnopyranoside, the latter being also known as Kaempferitrin, an important constituent that works as a chemical marker for recognition of the plant species. These compounds possess structural characteristics that favor the inhibitory effect on alpha-glycosidase, an enzyme linked to the intestinal cell membrane that is responsible for catalyzing the final process in the digestion of carbohydrates. Pinafo *et al* (2019) (9) investigated the effects BF in association with Bisphenol A that is an abundant material used in the production of daily utilities, such as food cans, bottles, electronic advices and medical equipment. Authors showed that the plant was capable of reducing the Bisphenol A-induced glucose levels, and prevented the early glucose increase in control groups and Bisphenol A-group. *In vitro* studies using a flavonoid-containing methanolic extract have shown that as well as the inhibition of alpha-glucosidase, alpha-amylase inhibition is considered as a key point for the treatment of hyperglycemia and diabetes. The results showed that the methanolic extract inhibited 55.2% of alpha-glycosidase activity and 67.7% of alpha-amylase activity, noting that the increase in the enzymatic inhibitory effect depends on the number and position of the hydroxyls contained in the flavonoids (Picot and Mahomoodally 2017;

Franco *et al*., 2017). Curcio *et al* (2012) investigated the effects of *Bauhinia forficate* in female with or without diabetes and showed that reduction in the glycemia in the treated group. Furthermore, the treatment contributed with the weight recovery. Cunha *et al* (2010) also showed hypoglycemic effects of this plant in diabetic rats for 7 days. Córdova-Maringel *et al* (2019) evaluated the effects of *BF* tea (0.4% of the plant/200 mL of water/ twice a day/ 3 months) in twenty-five type 2 Diabetes mellitus patients on lipid profiles and found significant reduction in total cholesterol and triglycerides levels. There was also reduction in the glycemia levels, but without statistical significance. Salgueiro *et al* (2016) did not observe regulation of glycemia in diabetic mice treated with *Bauhinia forficata.* Miceli *et al* (2016) and Farad *et al* (2015) showed *in vitro* anti-hyperglycemic effects of BF. Another pharmacological potential of the plant is its antiglycation property. The use of hexane and ethanolic extract containing flavonoids and phenolic acids demonstrated antiglycation activity higher than 50% in a study with Wistar rats with alloxan-induced diabetes, which is beneficial mainly for the treatment of diabetes, since the chronic increase of serum glucose levels trigger the oxidation of lipids and proteins that will lead in future cell damage (Franco *et al*., 2018; Oyeni *et al*., 2015).

Antioxidant activity

BF also demonstrate antioxidant action, as shown by the study of Silva and López (2015) in which diabetic animals presented a significant reduction of free radicals in the serum after the administration of BF. A significant reduction of free radicals in the serum was also observed after administration of the n-butanolic fraction of BF extract (Marques *et al*., 2013)and the occurrence of partial impairment of lipid peroxidation by Fe^{2+}, corresponding to the presence of gallic acid and quercetin compounds (Ecker *et al*., 2015). The mechanism of action of antioxidant bioactives such as flavonoids is due to their tendency to donate hydrogens and consequently to reduce highly oxidizing free radicals (Souza *et al*., 2018). As ponted above in this text, Pinafo *et al* (2019) investigated the effects BF in association with Bisphenol A. This compound increased the levels of malondialdehyde in the liver and decreased the catalase activity, thus leading liver oxidative stress. The use of the plant decreased malondialdehyde levels without modifying the catalase activity. This antioxidant property occurs due to the presence of flavonoids such as kaempferol and myricetin.
Sampaio *et al* (2019) showed antioxidant effects of *BF* extract in the genital system of male Wistar rats. In this study new compounds were identified in the extract: liquiritigenin, trans-caffeic acid, gallocatechin, and 2,4,6-trihydroxyphenanthren-2-glycoside. Franco *et al* (2018) showed antioxidant effects of the ethanolic extract of *BF* as well as anti-glycation activity. Miceli *et al* (2016), Farad *et al* (2015) and Sayago *et al* (2015) showed *in vitro* anti-oxidant effects of BF. Salgueiro *et al* (2016) evaluated the effects of this plant in diabetic mice and showed effectivess in normalizing the increase of Reactive Oxygen Species and lipid peroxidation. They also observed partial reduction of carbonylated protein levels that are commonly augmented in diabetic animals.

Anti-inflammatory activity

The anti-inflammatory effect of *BF* is a result of the presence of flavonoids and may act on the mediators involved in the inflammatory process. It may reduce the release of histamine and lead to inhibition of phosphodiesterases and protein kinases in the occurrence of modulation of cells involved with inflammation (inhibition of mast cell proliferation, T cells, B cells, NK cells, and neutrophils), inhibition of cytokine synthesis such as TNF-α. It can also be associated to inhibitory effect in enzymes present in the arachidonic acid pathway such as phospholipase A2, cyclooxygenase and lipoxygenase (Souza *et al*., 2018). The structure/activity ratio responsible for the anti-inflammatory effect is due to the molecular structure of flavonoids, such as C-ring unsaturation (2 to 3 positions), number and position of hydroxyl groups, C-4 carbonyl (Ring B), and glycosylation of the molecule (Souza *et al*., 2018). One of the BF compounds, quercitrin-3-rhamnoside confer anti-inflammatory properties to the plant extracts (Santos, Fortunato, Spotorno, 2019).

Antitumoral activity

BF lectins (BFL) is a monomeric glycoprotein with a molecular weight of 27.8 kDa and have two bioactive n-glycosylation sites which are found in BF stock tissues as the seeds of their fruits. This lectin has been arousing interest by having the antiproliferative and inhibitory potential of adhesion of several lines of tumor cells. (Silva *et al*., 2014). In a study conducted by Lubkowski (2017), BFL was shown to be cytostatic for several cancer cell lines, especially for melanoma cancer cells, which inhibited this potential to more than 95%. Silva Pinto *et al* (2019)described and characterized a new BF lectin, BfL-II from the seeds of the plant. Authors evaluated (*in vitro*) the antiproliferative activity of this new compound against human colorectal and breast cancer cells and observed significant reduction the proliferation of both cell lines. Silva *et al*. (2014) reported that BFL possesses antitumor property in human breast cancer cells, and the mechanism of action can be explained by the induction of cell death with inhibition of caspase-9, DNA fragmentation, resulting in the stop of the cell cycle. The anticarcinogenic effect can also be seen in the study by Silva and López (2015) in which BFL exhibited a broad spectrum of antiproliferative and pro-apoptotic activity on human hepatocellular carcinoma cells, thus constituting a promising candidate for the treatment of hepatocellular carcinoma human. It is important to note that BFL has no apoptotic potential for cells of normal viability, demonstrating selective for typically abnormal cells, which confers a differential about commonly used cytotoxic drugs that do not differentiate normal tissues from metastatic tissues (Silva *et al*., 2014). The promising antiproliferative effects of BF may be studied and applied in the development of new anticancer therapeutic approaches.

Antimicrobial activity

BF is known to show antifungal properties. Marques *et al*. (2013) showed that the extract obtained from the stem of this plant exhibited moderately active activity against *Epidermophyton floccosum* and the bark extract was active for all species *Microsporumcanis, Trichophyton Mentagrophytes, Trichophyton rubrum,* and *Epidermophyton Floccosum.* The antibacterial activity of the extract of BFstem bark was shown to be inactive and did not show growth inhibition halos of strains of *Klebsiella pneumoniae, Escherichia coli,* and *Staphylococcus* (Simões *et al*., 2014). However, it was found antibacterial activity in the study of Rocha *et al*. (2013), by the microdilution technique against *S. aureus*. Souza *et al* (2019) evaluated the antimicrobial effects of the ethanoic extract of

BF and showed that it could modulate the norfloxacin-resistance against *Staphylococcus aureus* SA1199-B. The mechanism of antibacterial properties of the flavonoids found in BF has not yet been completely elucidated. It is possibly due to the action in multiple cellular targets and not in a specific site, such as through damage to the cytoplasmic membrane, inhibition of synthesis of nucleic acids, inhibition of energy metabolism, inhibition of cell wall synthesis and inhibition of cell membrane synthesis.Furthermore,, the antibacterial effect restricted only to strains of gram-positive bacteria is due to the peculiarities between the cell walls of gram-positive microorganisms and gram-negative bacteria. This occurs possibly due to the relatively simple structure, and high polarity of the wall of gram-positive bacteria favors the entry of substances into these cells, while the structural complexity of the wall of gram-negative bacteria represents a major barrier to penetration (Gasparetto, 2014).

Diuretic activity

Souza *et al*. (2017) studied the diuretic actions attributed to the chemical constituents of *BF such* as canpherolic and quercetin glycosides. Diuretic action could be shown through the general activity test, where the crude extract of the plant was administered orally in preclinical trials in normotensive and spontaneously hypertensive Wistar rats. The main constituent identified as responsible for diuretic action is kaempferitrin, and the study suggested that *BF* extracts significantly increased urinary volume and electrolyte levels without altering pH or density parameters. In addition to increasing the urinary index, it showed an anti-natriuretic action and anti-kaliuretic action, thus exerting an increase of diuresis, but, saving sodium and potassium, also, kaempferitrin increased urinary creatinine and excretion of prostaglandin E2 without modifying calcium levels. Kaempferitrin-induced diuresis was not affected by the use of a non-selective inhibitor of nitric oxide synthesis nor by the nonselective muscarinic antagonist. Furthermore, a cyclooxygenase inhibitor was able to decrease its effect, suggesting that the diuretic and natriuretic properties of kaempferitrin are associated with the generation of endogenous prostanoids.

Anticoagulant activity

The anticoagulant activity of *BF* was confirmed by the neutralization of venous coagulation of *Bothrops Jaracussu* and *Crotalus Durissus Terrificus* in human plasma (Silva, López, 2015). The anticoagulant and antifibrinogenic effect are due to the inhibition of the serine protease enzymes involved in the blood coagulation disorders by the BF (Marques *et al*., 2013). Cechinel-Zanchett *et al* (2019) studied the vascular effects of BF extract and its main compound kaempferitrin, and its aglycone form kaempferol, in aortic rings of normotensive and hypertensive rats. Their results showed that, although kaempferitrin is the most common component in both methanolic and butanolic extract, only this last one showed endothelium-dependent and also independent vaso-relaxant properties.

Antiulcer activity

The antiulcer properties using an infusion of fresh leaves of *BF* were demonstrated after the induction of gastric ulcers induced by the HCl-Ethanol model administration in Wistar rats. The antiulcerogenic activity was attributed to the significant promotion of gastric mucus and the gastroprotective effect of the flavonoids contained in the aqueous extract of BF (Guimarães *et al*., 2015).

Conclusion

Studies with BF have demonstrated the presence of a wide variety of bioactive compounds, especially free and glycosylated flavonoids, which represent a feature of great interest in treating various pathologies. Some of the beneficial pharmacological effects show that this plant may play an important role as hypoglycemic, anti-oxidant, anti-inflammatory, antitumor, antimicrobial, anticoagulant, diuretic, anti-inflammatory, antiulcerogenic, and against Alzheimer's disease. BF represents a plant resource of great importance for the development of new medicines and nutritional products in the area of Ethnopharmacology. However, it is considered that more studies regarding the toxicity of this plant should be performed to establish the effectiveness and safety of its use.

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