The influence of using *Bauhinia forficata* Link in glycemic, lipid and toxicological profile in *in vivo* experimental models: A systematic review

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*Bauhinia forficata* Link, popularly known as ‘cow’s paw’, is characterized as a plant species widely used in traditional medicine as hypoglycemic. Given its high empirical use for therapeutic purposes coupled with the high interest in research with this plant species, this study aimed to perform a systematic review on *B. forficata* L. seeking for evidence-based information on the influence of the use of this plant in glycemic, lipid and toxicological profile in *in vivo* experimental models, using a secondary survey of experimental studies conducted and published on this plant species. A search strategy was established and a total of 36 articles were found in the search, after exclusion of duplicate articles and application of inclusion criteria, only 12 were evaluated in detail. The glucose dosing was the most performed biochemical determination, found in 100% of the studies. Most articles proved the hypoglycemic action of preparations from *B. forficata* L. Regarding the influence on lipid parameters, there were discordant results, and concerning toxicity, few articles on the subject were found, but the results indicated that the use of the aqueous extract from the plant is safe. Thus, it was possible to demonstrate the pharmacological potential of this plant species.

Key words: *Bauhinia forficata* Link, diabetes, hypoglycemic, systematic review.

INTRODUCTION

The history of pharmacy and medicines evolution is marked by the use of plants for medicinal and therapeutic purposes. Over the years, the scientific proof of the existence of pharmacological actions derived from plant species became real and this fact, combined with the excellent benefit-cost ratio in the production and processing of medicinal plants and the importance of this sector in primary health care, led this area to become the subject of intense research and investments by the herbal industry and also government institutions (Siani, 2003; Souza et al., 2009).

This scenario led to the adoption, in July 2006, of the...
Medicinal Plants and Herbal Medicines National Policy by the federal government and later the disclosure, by the Ministry of Health, of the National List of Medicinal Plants of Interest to the National Health System (RENISUS) whose aim is to direct scientific research in the area. This list includes 71 plant species with potential to generate herbal medicines which may be provided by the Unified Health System (SUS) (Brazil, 2009).

*Bauhinia forficata* Link is in this list and is one of the most studied species in Brazil, because of its broad popular use as an aid in the treatment of diabetes and also for its wide geographic distribution (Pizzolatti et al., 2003; Vaz and Tozzi, 2005). It is popularly known as ‘cow paw’ due to the characteristic bilobulated aspect of its leaves (Cunha et al., 2010).

In the current therapy, many drugs are used to manage diabetes, however, the perfect glycemic control is rarely achieved. Thus, the search for complementary therapies is very common (Silva et al., 2002; Souza et al., 2004). The difficulty in its treatment occurs, because this pathological condition is multifactorial and causes disturbances in the metabolism of carbohydrates, lipids and proteins. It is characterized by the maintenance of elevated blood glucose levels and total or partial absence of insulin and/or functional deficiency of receptors during the glucose absorption, which are factors that may promote this condition (DSBD, 2009).

Given the complexity of this metabolic disease, associated with the high empirical use of *B. forficata* L. for therapeutic purposes by the population and the high interest in research with this plant species, this study aimed to perform a systematic review on *B. forficata* L. seeking evidence-based information on the influence of the use of this plant in the glycemic, lipid and toxicological profile in *in vivo* experimental models, using, for this purpose, a secondary survey of experimental studies conducted and published on this plant species.

**MATERIALS AND METHODS**

The search strategy sought to achieve experimental articles in the literature that studied the effects of using preparations from *B. forficata* L. in animal and humans’ biochemical levels. The articles were researched in the database of the Virtual Health Library (VHL) of BIREME, using the word *B. forficata* as a descriptor. All this survey took place between January 7 and 8th, 2013.

Initially, the analysis of the titles and abstracts of the articles found was performed as a way of choosing studies of significant relevance to the research. The repeated and non relevant studies were excluded at this point. After this step, the articles chosen were fully analyzed and those that fit the following inclusion criteria established (articles from experimental research related to the possible changes in the biochemical parameters of humans and animals caused by the use of preparations from *B. forficata* L.) were selected. There was no restriction regarding the publication date or language, and review studies were excluded.

All analyzes were independently performed by two authors and the disagreements that occurred by chance were resolved by consensus between the researchers or evaluation by a third author.

**RESULTS AND DISCUSSION**

A total of 36 articles were found in the search, and after exclusion of duplicate articles and application of inclusion criteria, only 13 were evaluated in detail. Figure 1 shows a schema on the choice of the articles included in this study.

**Biochemical measurements analyzed in response to the use of *B. forficata* L.**

The analysis of the articles included in this study showed that the determination of plasma glucose, in order to investigate the hypoglycemic action arising from *B. forficata* L. preparations, was present in 100% of the studies. Changes in lipid profile were also evaluated from measurements of triglycerides and total cholesterol and its fractions. In addition to these analyzes, there were also found studies that conducted enzyme dosing to investigate the antioxidant action and toxicity of the preparations obtained from this plant species. An overview of the frequency of these biochemical determinations in the articles analyzed is as shown in Figure 2.

These studies were conducted in different experimental models and using different extractive methods. However, the leaves were the part of the plant used in all experiments. This reflects the fact that this plant species is widely used empirically by the population in the form of tea from its leaves.

The popular knowledge about the use of this plant as an adjunct to the treatment of diabetes motivated the studies found in the literature. Table 1 shows the studies that evaluated various biochemical parameters in response to the use of *B. forficata* Link in different experimental models.

**Glycemic profile**

The results of the glycemic parameters showed that the use of aqueous, ethanol, hexane and hydroethanolic extracts, and n-butanol fraction from the leaves of *B. forficata* L. was able to reduce the hyperglycemic state in both mice and humans, demonstrating the ethnopharmacological value of this plant for this purpose. However, when the glycemia in diabetic rats on gestational period was assessed, there was no decrease in this parameter. This fact can be explained by factors such as, the experimental protocol used, the methodology for obtaining extracts, environmental, seasonal and collection of the plant conditions, besides the cultivation and storage...
of it. All these factors may qualitatively and quantitatively influence the presence of the plant’s characteristic metabolites that are important to the development of pharmacological action, among which kaempferol and quercetin glycosides stand out (Silva et al., 2002; Pepato et al., 2010; Souza et al., 2010).
Table 1. Studies evaluating the behavior of biochemical parameters in response to the use of * Bauhinia forficata  Link.*

| Reference       | Method used                                                                 | Result                                                                 |
|-----------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Silva et al. (2002) | ES*: N-butanol fraction of the hydroalcoholic extract from the leaves; EM**: alloxan monohydrate-induced diabetic and nondiabetic Swiss albino mice; BPE***: Glycemia. | Reduction of blood glucose in both diabetic and nondiabetic mice.       |
| Pepato et al. (2002) | ES: Aqueous extract (decoction of the leaves, 150 g/L); EM: Streptozotocin-induced diabetic and nondiabetic wistar rats; BPE: Plasmatic and urinary glucose, urea, urine volume, triglycerides and cholesterol - chronic administration - 31 days orally. | Diabetic rats: reduction of glycemia, glycosuria, urea and urine volume. There was no significant reduction of cholesterol and triglycerides. |
| Pepato et al. (2004) | ES: Aqueous extract (decoction of the leaves, 150 g/L); EM: Streptozotocin-induced diabetic and nondiabetic wistar rats; BPE: Lactate dehydrogenase, creatine kinase, amylase, and angiotensin and bilirubin converting enzyme - chronic administration - 33 days orally. | There were no changes in the evaluated parameters, showing safety on the use of the tea. |
| Jorge et al. (2004) | ES: N-butanol fraction of the leaves' hydroethanolic extract, from which the kaempferitrin used in the experiment was isolated; EM: Alloxan-induced diabetic Wistar rats; BPE: Plasma and urinary glucose - acute administration – 24 h (glucose) and 3 h (glycosuria) - orally. | Significant reduction of glycemia, but the glycosuria showed no difference. |
| Lino et al. (2004) | ES: Aqueous, ethanolic and hexane extract; EM: Alloxan-induced diabetic Wistar rats; BPE: Glycemia, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, acute administration - 7 days orally. | Reduction of glycemia, triglycerides, total cholesterol and HDL cholesterol. The LDL cholesterol showed no reduction. |
| Souza et al. (2004) | ES: N-butanol fraction of the leaves' hydroethanolic extract, from which the kaempferitrin used in the experiment was isolated; EM: Alloxan-induced diabetic and nondiabetic mice; BPE: Glycemia. | Reduction of glycemia in diabetic and nondiabetic mice. |
| Vasconcelos et al. (2004) | ES: Aqueous extract (infusion); EM: Tityus serrulatus scorpion venom (TSV)-induced hyperglycemic Wistar rats; BPE: Glycemia, catecholamines (norepinephrine and epinephrine); acute administration - 6 h orally. | Reduction of glycemia. However, it did not reduce the level of catecholamines. |
| Damasceno et al. (2004) | ES: Aqueous extract from the leaves; EM: Streptozotocin-induced diabetic and nondiabetic female Wistar rats, both in gestational period; BPE: Glycemia, cholesterol, triglycerides and total protein, uric acid, glutathione (GSH); chronic administration - 21 days orally. | There was no hyperglycemia, hypertriglyceridemia or maternal hypercholesterolemia control nor influences on the level of proteins. There was a reduction of uric acid and increased GSH. |
| Menezes et al. (2007) | ES: Aqueous extract from the leaves; EM: Normoglycemic mice; BPE: Glycemia; acute administration – 8 h orally. | Glycemia reduction. |
| Volpato et al. (2008) | ES: Aqueous extract from the leaves; EM: Streptozotocin-induced diabetic and nondiabetic female Wistar rats, both in gestational period; BPE: Glycemia, GSH, superoxide dismutase (SOD), chronic administration - 21 days orally. | There was no reduction of glycemia, and SOD levels did not get influenced by the use of the extract. The levels of GSH increased. |
Table 1. Contd.

| Study (Year) | ES: Aqueous extract from the leaves (infusion); | EM: Human patients with Diabetes Mellitus type 2; | BPE: Glycemia; chronic administration - 75 days – orally. | There was glycemia reduction. |
|--------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------|
| Moraes et al. (2010) | ES: Hydroalcoholic extract from the leaves, then dried in an oven and in spray dryer and in the form of granules. | EM: Streptozotocin-induced diabetic and nondiabetic Wistar rats; | BPE: Glycemia; acute administration – 7 days - orally. | There was glycemia reduction. |
| Cunha et al. (2010) | ES: Aqueous extract; | EM: Diabetic and nondiabetic mice; | BPE: Glycemia, proteinuria, chronic administration - 20 days - orally. | There was a decrease of glycemia and proteinuria. |

*ES: Extractive Solution; **EM: Experimental Model; ***BPE: Biochemical Parameters Evaluated.

The aforementioned variables, when compared among studies, are not significant to justify the results found, however there are rats’ "pregnancy status" factor that hindered the reduction of glycemia in some way, since only in these cases there was no improvement on hyperglycemia not even when higher doses of the extract were used. Although, there was no glycemia reduction, the use by pregnant rats shows that the plant extract was safe for both maternal and fetal outcomes, not altering the maternal reproductive outcome or the fetus and placenta development in the diabetic group (Damasceno et al., 2004; Volpato et al., 2008).

The treatment of diabetic rats with *B. forficata* aqueous extract did not only reduced plasma glucose, but also urinary glucose, urea, uric acid, urinary volume and proteinuria, which demonstrates a reduction in problems related to carbohydrate and protein metabolism, which are common under conditions of hyperglycemia, suggesting a possible clinical application of this plant for the treatment of diabetes (Damasceno et al., 2004; Lino et al., 2004; Pepato et al., 2002; Curcio et al., 2012). Discordant results were found by Jorge et al. (2004) regarding glucosuria, which showed no reduction after treatment with a compound isolated from the plant, Kaempferitrin. This result can be attributed to the acute treatment used, since the studies which indicated a reduction in this parameter used a chronic treatment, but also by having used a different fraction of the plant.

Lipid profile

Most studies assessing the lipid profile did not detect changes in these parameters after using the plant (Pepato et al., 2002; Damasceno et al., 2004). However, Lino et al. (2004) showed a reduction in three parameters: total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol. The decrease in HDL cholesterol is not a good result when the risk of dyslipidemia and cardiovascular diseases is considered, which often accompany diabetes patients, but more studies are needed to assess these parameters, since there are few articles on it and the results presented disagreements.

**Toxicological profile**

The toxicity of the decoction from the leaves of *B. forficata* L. was studied by determining the serum activities of enzymes known as reliable markers of toxicity. These enzymes were monitored in normal and streptozotocin-induced diabetic rats to find out if the use of this plant species as decoction presents toxic effects in muscle tissue, pancreas or liver or in the renal microcirculation (Pepato et al., 2004).

The results for plasma bilirubin, lactate dehydrogenase, creatine kinase and amylase did not show any significant changes, which leads to the inference that the improvements in glycemia occur without damage to the liver, bile ducts and muscles, to the cells in general and to the pancreas (Stanely et al., 2000; Mansour et al., 2002; Pepato et al., 2004).

The plasma dosage of angiotensin converting enzyme also showed no changes in this study. The determination of this enzyme’s activity has been suggested as an indicator of microangiopathy in diabetic patients, so the extract also proved safe for this determination (Lieberman and Sastre, 1980; Toop et al., 1986; Pepato et al., 2004).

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Through this systematic review, it was possible to demonstrate the high pharmacological potential of *B. forficata* L. as an aid to the treatment of diabetes, since most studies have demonstrated their effective action in lowering plasma glucose levels even when studying its action in humans.
Moreover, it was shown that the use of aqueous extract from this plant species is secure as it did not promote any tissue toxicity detectable by specific biomarkers nor changes the maternal reproductive system and fetal development when its continued use was assessed in pregnant rats. The value of this plant in pharmacological therapy is being studied and its use is very promising for the design of new pharmaceutical forms, taking advantage of the rich biodiversity that our country presents.

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