



Diabetes, What is the Benefit in the Use of Medicinal Plants as an Optional form Adjuvant to Medicines? A Systematic Review

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Authors' contributions

The short systematic review study was carried out in collaboration among all authors. Authors IDS, VAN and EMR wrote the first draft of the manuscript. Authors FJMR, HVR collected information about the plant. Authors IDS and EMR collected information about diabetes. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To present a description of the benefits in the use of three plant models, in this case, *Bauhinia forficata*, *Eleusine Indica* and *Orthosiphon stamineus Benth* in the antidiabetic actions addressed through its mechanism of pharmacological and antioxidant action.

Methodology: In this study, the systematic review methods was used.

Results: The extracted studies totaled 146 randomized and experimental articles with rats and animals, at the end of the study extraction, only six covered all inclusion criteria and were used in the short review.

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Conclusion: This systematic short review on the use of *Bauhinia Forficata*, *Eleusine Indica* and *Orthosiphon Stamineus Benth* verified the ability to reduce the hyperglycemia of these plants in association with drug treatment in diabetic patients and, thus, brings a promising answer by decreasing worsening and has protective enzymatic and antioxidant activities thus, it favors the reduction of hyperglycemia.

Keywords: *Bauhinia forficata*; *synadenium grantii hook F*; *orthosiphon stamineus benth*; *diabetes*; *hyperglycemia*.

1. INTRODUCTION

The World Health Organization (WHO) reports as a risk factor for developing diabetes [1], mainly related to disorders caused in lipid metabolism [2,1] and in type II diabetes mellitus there is a reduction in tissue sensitivity to insulin caused by the absence of insulin secretion and it is called a syndrome of impairment of carbohydrate [3] fat and protein metabolism [4,1]. The pathophysiology of type II diabetes occurs through the use of glucose as a signal for the pancreas to release insulin through the β cells of the langheranos and when the individual does not have glucose in the cells [5,6] the body begins to obtain energy from another source, and starts using lipids in metabolic actions [7,8] and this process is considered a disturbance in the glucose metabolism of the body, where the glucose present in the blood is excreted in the urine without being used as a nutrient by the body [8,9]. In the last ten years, type II diabetes has been associated with increased mortality and a high risk of developing macrovascular or microvascular complications associated with neuropathies [10,11,12]. We can cite blindness, renal failure, amputation of limbs as the main complications which bring excessive health expenditures to the Brazilian public health system and considerable reduction in works capacity and life expectancy [5,13]. In the last ten years in Brazil, 10% of young adults over the age of 18 years old had a diagnosis of diabetes, which is directly related to about 1.5 million deaths [14]. Thus, type II diabetes has been considered a worldwide epidemic and a major challenge for the health system worldwide [15,14] and in the last year, phytotherapy has been used to treat type II diabetes in a adjunctive way to the drug treatment and the use of phytotherapy has been used exponentially mainly in industrialized countries and the increase in the use of plants adjuvant to the treatment of medicated diabetes is related to good social acceptance and mainly to the belief in the innocuity of natural products compared to

other products of synthetic origin [11,12] and its highest use is related to the easy access to these products due to online sale, exemption from medical prescription and large commercial areas and the reclude number of information about the potential adverse effects that confirm the illusory feeling of security [6,9] and due to these problems previously established in the paragraphs, this short and systematic review study aims to present a description of the benefits in the use of three plant models, in this case, *Bauhinia forficata*, *Eleusine indica* and *Orthosiphon stamineus Benth* in the antidiabetic actions addressed through of its pharmacological and antioxidant mechanism of action.

2. METHODOLOGY

The methods used to construct this study was a short systematic review according to Cochrane protocols. The articles included were these published between 2004 and 2018 and the search was carried out in the electronic databases SCOPUS, PUBMED, COCHRANE and MEDLINE. The search for the articles was divided into two phases, in the first phase the group used the terms related to the species of interest of the plant used in the treatment [*Bauhinia forficata*, *Synadenium grantii Hook F.* and *Orthosiphon stamineus Benth*] in the second phase the group was considered the terms related to the primary outcome of interest to the study and these primary outcomes were considered the inclusion criteria in the short and systematic review [Diabetes, pharmacological actions, antidiabetic actions, antioxidant actions and angiogenic neuroprotective and protective actions, rats, humans and hyperglycemia]. To achieve the results according to the primary outcome, the combination in each group of Boolean operators "OR", "AND" and "AND NOT" was used. Original, experimental and randomized articles in English and Portuguese were included in these short review studies, and extended abstracts were excluded as well as studies considered gray literature. The initial process of searching for studies started by

reading the titles and abstracts by three researchers independently and, thus, a research base was formed in the theoretical construction of the systematic short review. Articles without an abstract and without complete information according to the inclusion criteria related to primary outcomes were excluded from this short review. The studies that presented divergences were selected by a fourth reviewer. The methodology used in this study was very heterogeneous. As a result, it was not possible to determine all the data for each of the studies. This was due to the lack of details in the methodology used by the included studies and in other sections of the text of the included studies. Therefore, it was not possible to perform a complete statistic with data and results analysis showing relative numbers. This short review was built according to the methodology of how the use of plants benefits in the treatment of type II diabetes considering the pharmacological and antioxidant actions in the treatment of type II diabetes as the primary outcome.

3. RESULTS AND DISCUSSION

3.1 Critical Analysis

3.1.1 *Bauhinia forficata*

Bauhinia Forficata belongs to the genus of *Bauhinia*, and received this scientific name in order to honor the Franco-Swiss botanist Gaspar Bauhin. Currently, there are more than 300 species widely distributed in tropical and subtropical forests, and around 64 species are found in several Brazilian regions [16]. This species is usually known as “cow’s foot” or “cow’s claw” due to its leaf design which are usually composed of two leaflets joined at the base [16]. This species is used in folk medicine to treat different types of pathologies, in this case, leaves and stem are used, mainly in diabetes, infection, pain and initial inflammatory processes [3]. In the last decade, interest in *Bauhiniaforficata* has increased considerably in the world as a result of experimental studies with positive responses in its ethnopharmacological observations [17]. The *Bauhinia forficata* presents leaves with measures around 7 to 12 cm in length with a striking feature when divided into two large lobes, in this case, the apex of the lobes are sharp and acuminate and their leaf margin is smooth. Its flowers are zygomorphs arranged in axillary racemes with variation in color, according to the species and subspecies, that is, it may present with a white or

pink color. Its fruits are known with flattened and dehiscent vegetables or pods of the linear type [17] and its seeds maintain the flatness but have pores, with approximately 1cm with a characteristic brown to black coloration and its trunk is tortuous from 30 to 40 cm in diameter [1] (Fig. 1).



Fig. 1. *Bauhinia forficata*

3.1.2 *Eleusine indica*

Eleusine Indica popularly known as chicken grass, orchard grass, chicken leg, donkey grass, parrot foot widely recognized in Brazilian agriculture as an infesting weed and brings problems to agriculture in more than 50 countries in the world [18,19]. *Eleusine indica* is native to Africa and is currently spread across all Brazilian and tropical regions. It is a very common plant in annual and continuous cultivation and occurs in all types of environments altered due to agriculture and presents itself aggressively in natural pasture cultures in the form of infestation [19]. *Eleusine indica* is recognized for its terminal inflorescence with vertical formation with several spikelets distributed on a single side of the rachis. A well-developed root system is constituted, and is generally found as one of the main weeds of compacted soils as in no-till [18,19]. Chicken grass has therapeutic properties and has been used in recent years in an efficient way to treat respiratory diseases and to control hyperglycemia, especially in type II diabetes [19] (Fig. 2).



Fig. 2. *Eleusine indica*

Table 1. Identification of selected articles for short systematic review

Author	Article Identification	Year
RAO NK, KRUPAVARAM B, SREENIVAS PS, SHARMILA R. Antidiabetic activity of Orthosiphon Stamineus Benth Roots in Streptozotocin induced type 2 diabetic rats. Asian J Pharm Clin Res. v.7. Issue 1. p.149-153.[20]	A1	2014
RAUDHAHTULNUR MZ, FAZLIN Z, RESNI M, JANNATHUL F, NOORZAID M.Does Orthosiphon stamineus Benth enhance GLUT4 translocation in the skeletal muscle of induced type II diabetic rats? v.8. Issue 7. p. 1061-1064. [21]	A2	2018
SALGUEIRO et al. Effects of Bauhinia forficata Tea on Oxidative Stress and Liver Damage in Diabetic Mice. OxidativemedicineandCellularLongevity. Article ID 8902954. 9 pages. [22]	A3	2016
DAMASCENO et al. Effect of Bauhinia forficata extract in diabetic pregnant rats: maternal repercussions. Phytomedicine. v.11. p.196-201. [15]	A4	2004
MOHAMMAD I, CHARLES G. Eleusine indica L. possesses antioxidant activity and precludes carbon tetrachloride (CCl ₄) -mediated oxidative hepatic damage in rats. Environ Health Prev. Med. v. 17. p.307–315. [18]	A5	2012
OKOKON JE, ODOMENA CS, IMABONG E, OBOT J, UDOBANG J. ANTIPLASMODIAL AND ANTIDIABETIC ACTIVITIES OF ELEUSINE INDICA. International Journal of Drug Development & Research. July-Sept. v.2. Issue 3. [23]	A6	2010

3.1.3 *Orthosiphon stamineus Benth*

Orthosiphon stamineus Benth belongs to the *Lamiaceae* family and is known in the general population as “Cat’s Mustache” in America it receives the name “Java Tea”, in Indonesia it is known as “Kumis Kuching” and in Malaysia and Vietnam it presents the following denominations “Misai Kuching” and “Râu Méo” [24]. This species is presented in the form of herbaceous shrub with fast growth which can reach 1 to 2 meters in heights and have a width equivalent to 1 meter [25,24]. The plant is characterized by racemes equivalent to 10 to 20 meters in length and with exuberant tubular and unique flowers and its stamens are 5 to 6 centimeters that resembles cat whiskers, hence the use as a common name. Its cultivation occurs in Southwest Asia, Australia and Africa [25]. This species has been used traditionally for many centuries to treat kidney disease, bladder stones, urinary tract infection, liver and bladder changes, rheumatism, diabetes and gout [25,24].

For example, in Vietnam for about 10 years this species has been used to treat kidney inflammation, kidney stones and dysuria [24]. Still, the leaves and roots are used as tea to

reduce cholesterol and blood pressure [25,24]. Recently, other effects have been reported in a beneficial way such as anti-diabetic, anti-inflammatory, antiproliferative and anti-angiogenic activity [25]. However, until now, the constituents with chemical characteristics of this plant have not been clarified in detail [24]. But this species has a metabolic effect, for example, it increases the secretion of insulin in the pancreas of perfused rats, as mentioned by Sriplang et al. (2007) in their experimental study and its crude extract demonstrates a beneficial antidiabetic effect in diabetic rats with streptozotocin (STZ) [24].



Fig. 3. *Orthosiphon stamineus Benth*

3.2 Identification of the Studies Included in the Short Systematic Review

The extracted studies totaled 146 randomized and experimental articles with rats and animals, at the end of the study extraction, only six covered all the inclusion criteria and were used in the short review (Table 1).

4. PHARMACOLOGICAL ACTIVITY RELATED TO ANTIDIABETIC ACTION

Therapeutic plants in a sufficient amount of nutrients play an important role in the development of a healthy organism [14]. Plants such as *Orthosiphon Stamineus Benth*, *Eleusine indica* and *Bauhinia forficata* are nutraceutical and are related to ideal human consumption as food or treatment that acts as a beneficial effect of physical condition and disease prevention in humans [15,18,23,20,21,22]. It is possible to observe in the studies included in this short review that plants such as *Orthosiphon stamineus Benth*, *Eleusine indica* and *Bauhinia forficata* were made from natural molecules preferable to the benefit of health in the optional control of medications in type II diabetes [15,18,23,20,21,22]. *Eleusine indica* with negligible acute toxicity presents alkaloids, terpenes, flavonoids, tannins, anthraquinones, saponins and cardiac glycosides and thus demonstrates a significant medicinal value of this plant traditionally used in Brazilian folk medicine [18,23]. It is possible to verify in the studies included in this short review that the photochemical actions for the anti-diabetic activity of *Eleusine indica* through the use of the leaf extract showed the presence of terpenes, tannins, flobatanins and anthraquinones [18,23]. And these photochemical actions for antidiabetic activity have been proven in the studies included in this short review through a metabolic action characterized by an apparent decrease in hyperglycemia and a significant improvement in the diabetic body weight [18,23].

The species of the genus *Bauhiana* is characterized by the accumulative presence of free and glycosylated flavonoids mainly in its leaves with a high content of β -sitosterol and kanferol-3,7-diramnoside and also the presence of a heteroside called bauhinoside found in its leaves and seeds [22]. And hyperglycemia is corrected by the mechanism of action related to the reduction of blood glycemia through the inhibition of the enzyme responsible for catalyzing the process of digestion of sugars and

is related to quercetin and canferol (kaempferol) [22], because, both have structures that favor their interaction with α -glycosity [22] and the use of dry extract through spray-drying and dry granules has shown hypoglycemic activity from concentrations equivalent to 200 mg/kg [22,13].

Orthosiphon stamineus Benth has a hypoglycemic action, the extract significantly decreases the plasma glucose concentration in a dose-dependent manner [15,22], for example, the total extract of 1.0 g/kg effectiveness in decreasing plasma glucose concentrations with parallel use of glibenclamide (5 mg/kg) [15,22]. As well, it demonstrated a decrease in triglycerides and it was possible to highlight that in the pancreas of rats perfused in the study included in this short systematic review, the extract did not increase insulin secretion in the presence of glucose [15,22], however, extracts of 100 g/ml have increased the potential for glucose-induced insulin secretion, that is, this species is effective in relieving hyperglycemia and improving the lipid profile [20,22]. The studies included in this short review demonstrated that *Orthosiphon stamineus Benth* with the presence of flavonoids and terpenoids has hepatoprotective and hypoglycemic activity [20,21]. Thus, it is possible to list the presence of glycosides, flavonoids, tannins, catechol and alkaloids with active actions in hypoglycemic plants and these molecules present antidiabetic activity through active fraction isolation [20,21]. The species activity depends on the extract dose, for example, the dose equivalent to 800 mg/Kg is comparable to the effect produced by glibenclamide [20,21]. In the studies included in this short review, it is possible to prove that the oral use of *Orthosiphon Stamineus Benth* with a dose of 800 mg/Kg significantly reduced blood glucose levels and did not show a significant difference with the antihyperglycemic effect produced by glibenclamide [20,21]. This indicates that the effect of the extract is not due to pancreatic stimulatory activity, but to the insulin mimetic activity of the extract [21].

5. ANTIOXIDANT ACTIONS

Diabetes mellitus is a metabolic disorder with several antioxidant changes linked to multiple etiologies and characterized by chronic hyperglycemia with severe disorders of carbohydrate, fat and protein metabolism that will result in changes in insulin secretion [15,18,23,20,21,22]. *Orthosiphon stamineus Benth* rich in flavonoids, terpenoids and

chromene caffeic acid derivatives with phenolic compounds show a reduction in the rate of glucose absorption and consequently cause antidiabetic activity [20,21], for example, the aqueous extract exerts antidiabetic actions on lower lipids through its free radical scavenging activity and partly to increase glucose metabolism [21]. In addition, this species has an inhibitory effect of gluc-glucosidase on the small intestine which breaks down non-absorbable oligosaccharides. This α -glucosidase inhibitor most commonly used in recent years is acarbose [20]. Acarbose is an oligosaccharide produced by cultivated strains of microorganisms with anti-competitive inhibitory functionality with greater affinity for sucrose than pancreatic β -amylase glucoamylase [20,21] and it appear to delay the rapid digestion of starch and sucrose, there by prolonging the time required for carbohydrate absorption [20,21]. In addition, it is possible to identify which acarbose type molecules that inhibit α -glucosidases, which are present in the small intestine epithelium, decrease postprandial hyperglycemia and improve impaired glucose metabolism without stimulating insulin secretion in patients with diabetes mellitus [20]. This species should be used for patients with an initial diagnosis of type II diabetes who has a blood glucose level slightly above the level considered alarming for diabetics [20,21] and parallel to the use of sulfonylurea (in this case, glibenclamide) or biguanide (metformin) thus avoiding the additional use of drugs to keep your blood glucose level within a safe range [20,21].

Orthosiphon stamineus Benth extracts in the studies included in this short review significantly reduced plasma glucose concentrations [20,21], so the extract may be beneficial for patients with diabetes mellitus [20]. We found in the studies included in this short review that the gluconeogenic liver enzyme or glucose 6-phosphatase (G6P) increased considerably in diabetic rats [20,21]. The treatment with *Orthosiphon Stamineus benth* in extract showed signs of significant reduction in G6P levels and this was due to the primary activities of modulation and regulation of G6P through the regulation of cyclic adenosine monophosphate 3'and 5' with any other metabolic activation and oxidative of gluconeogenesis or with the inhibition of glycolysis [20,21]. In other words, it improves the diabetic condition through extra pancreatic mechanisms [21].

Furthermore, *Bauhinia Fortificata* has secondary metabolites and protease inhibitors capable of

inhibiting a wide variety of proteolytic enzymes that include the protease of the plant itself and these proteolytic enzymes tend to delay the proteolysis of the cell walls and proteins of the plant's membrane thus reducing, cellular disorganization and hindering the penetration of pathogens preventing the mobilization of reserve proteins [15,22].

These proteolytic enzymes are used in the treatment of several human pathologies, as it inhibits proteases that play a strategic role in the human organism [15] and these proteolytic enzymes such as lectins that are proteins or glycoproteins that have a subunit link to a sugar site [22] are considered selective ligands for cells and glycoconjugates with the ability to specifically recognized and create reversible bonds with carbohydrates or substances that contain sugars, however without changing their covalent structure [15,22]. Furthermore, the lectins from *Bauhinia Fortificata* have a distinct chemical characteristic and exhibit agglutinating activity on several cell types which can inhibit the adhesion of bacteria or cancer cells to the tissue and thus interfere with the course of an infection and tumor progression [22].

Bauhinia Fortificata has shown clinical importance in the treatment for the Ministry of Health (SUS) with the purpose of managing resources in the worsening of complications in diabetic patients and, in this case, the Brazilian public health system [22], has used in popular medicine the *Bauhinia Fortificata* as a hypoglycemic, purgative, diuretic, antiarrheal, depurative and renal tonic medication [15,22] It is able to reduce urinary excretion in cases of polyuria and glycosuria, regulating blood glucose, especially in patients with diabetes mellitus II [20,22].The hypoglycemic function of this plant depends on the presence of kamferitrin [22]. Kamferitrin with its antioxidant potential isolated from the n-butanolic fraction of *Bauhinia Fortificata* has demonstrated in previous studies a reduction in the levels of free radicals in the serum of a diabetic animal model [15]. The chronic increase in blood glucose in diabetics triggers the oxidation of lipids and proteins that causes considerable cellular damage [22]. *Bauhinia Fortificata* acts as an important antioxidant as are protected the sulfhydryl groups of proteins from diabetic rats against lipid oxidation and peroxidation [15,22].

Eleusine indica has multi-biological antioxidant actions [15,22]. This species produces a high

number of naturally occurring secondary metabolites, with unique oxidative activities [15], and includes in this species the following metabolites, flavonoids, phenols, phenolic glycosides, saponins, cyanogenic glycosides, unsaturated lactones and glucosinolates [15,22]. This short review shows that there was a direct and significant relationship between the total phenolic molecular content and the free RSA of 2,2-diphenyl-2-picrylhydrazyl (DPPH) of the *Eleusine Indica* extract. This happens due to the greater presence of phenolic constituents and also the presence of other secondary metabolites such as glycosides and C-glycosylflavone. 2,2-diphenyl-2-picrylhydrazyl is a stable, synthetic nitrogen-free radical that accepts an electron or hydrogen radical in order to become a stable diamagnetic molecule [15,22]. This magnetic stability exhibits an elimination of strong free radicals with a direct effect that can result in favorable actions against pathological changes caused by diabetes mellitus specifically by the induced presence of carbon tetrachloride (Ccl₄) [15,22]. The studies included in this short review showed that *Eleusine Indica* avoids oxidative stress induced by the presence of Ccl₄ and inhibits liver damage. It is noteworthy that (Ccl₄) induced hepatotoxicity is a common model system and used to track plant extracts for activity hepatoprotective [18,23].

In the studies included in this short review that used *Eleusine Indica* in the treatment of diabetes, it was possible to verify a significant increase in serum levels of AST and ALT mainly after the administration of (Ccl₄) [18] However, these enzymes decreased after treatment with *Eleusine Indica*, which clearly demonstrates significant liver restoration [18]. It is possible to observe that two phospholipid membranes of the cellular and subcellular membranes are the main targets of free radicals in this liver restoration process [18,23]. In this case, the compound that inhibits membrane phospholipid peroxidation appear to have a protective oxidative pharmacological effect by preventing oxidative pathological events induced by radicals [23]. These studies included in this short review prove that lipid peroxidation implies in the pathogenesis of liver damage mainly by the free radical branching of Ccl₄ and thus causes damage to the cell membrane and subsequent to the release of hematotoxicity marker enzymes [18]. The treatment with *Eleusine Indica* prevents lipid peroxidation, this can happen due to the antioxidant elements that eliminate free radicals [23]. The studies included in this review were

able to demonstrates that the main important liver enzymes activated in the detoxification of lipid peroxides or known as reactive oxygen species (ROS) are; catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) [18]. And when oxidative stress occurs, reduced antioxidant Glutathione (GSH) is widely consumed by enzymes related to glutathione and results in the induction of intoxications [23]. The included studies that made use of *Eleusine Indica* it was is possible to prove that its protective action with a cellular constituent characteristic of oxidative damage acts as a natural enzyme antioxidant protector [14,15].

In short, *Eleusine Indica* has a significant hepatoprotective effect against type II diabetes mellitus and this protection can occurs at least in part through the oxidative damage induced [18], for example by Ccl₄ or other specific pathophysiological damage belonging to type II diabetes [23].

6. CONCLUSION

This systematic short review on the use of *Bauhiana forficata*, *Eleusine indica* and *Orthosiphon stamineus Benth* verified the ability to reduce the hyperglycemia of these plants in association with drug treatment in diabetic patients and, thus, brings a promising answer by decreasing worsening and has protective enzymatic and antioxidant activities thus, it favors the reduction of hyperglycemia. However, there is a need for further scientific research involving a greater number of patients with randomized, double-blind studies, mainly in the Brazilian population.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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