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Review Article

The Pharmacological Uses of *Cissus sicyoides*

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Abstract

One of the oldest practices of mankind is phytotherapy. The study of various plants has had fundamental stimulus so that, in this way, a great amount of phytotherapeutic compounds can be obtained that can be economically exploited. An example of such plants is *Cissus sicyoides*, also known as vegetable insulin, which has wide use in empirical treatment of diabetes as well as several other activities such as anti-inflammatory, antidiarrheal, anxiolytic, vasoconstricting, vasoprotective etc. The literature on these activities suggests the different activities or potential activities that can be used for treatment as a therapeutic agent or as an adjunct to therapies with established treatment, and there is no commercially available herbal medicine.

Keywords: Antidiabetic; *Cissus sicyoides*; Pharmacological Effect; Phytotherapy; Vasoprotective

Introduction

Phytotherapy is one of the oldest therapeutic practices of mankind, which is based on popular or botanical knowledge. The first discoveries were made in Iran and China, where compiled reports containing herbs and their phytotherapeutic capabilities were made available [1]. The World Health Organization (WHO) recognizes the importance of phytotherapy and suggests that it is a viable and important alternative, especially in developing countries, due to its low of production and use [2]. Furthermore, medicinal plants, pharmaceutical preparations and natural products that are isolated move a large market, both in industrialized countries and in those that are still emerging. Despite the wide use of plants by the population, the pharmacological studies still lack studies that prove many of their activities, since there is the variability of the species between the regions and between countries [3].

Vegetable insulin (*Cissus sicyoides*) is located in the Amazon region, in Brazil, that belongs to the family Vitaceae [4] and is a genus of greater predominance in South America [5]. The species has ovate-cordiformes leaves, having as fruit a black berry, that contains a seed. The main use by the population is through tea through infusion, used for the treatment of diabetes [6].

Vegetable insulin has several uses. In Brazilian, it is a popular medicine and used as anti-inflammatory, antipyretic and antidiabetic drug. It also possesses antibacterial, antiallergic, cytostatic and gastroprotective effects [4]. Among its composition flavonoids, alkaloids, saponins, steroids, phenolic compounds and anthocyanidins, which are mainly responsible for the activities that the plant exhibits [6]. The anthocyanidins present in its seed are primarily responsible for its use in the dye industry [7].

This review explores the phytotherapeutic abilities of Vegetable insulin as a treatment agent for various conditions.

Phytochemical study

Dias., *et al*. [8] conducted a research on the secondary metabolites, where were used methodologies for the identification of saponins, steroids, tannins and other metabolites that are mainly responsible for the action that the plant presents. In addition, the study evidenced the absence of alkaloids, which has also been shown in previous phytochemical studies [10]. Table 1 shows the result of the methodologies made for identification. Table 1 shows the metabolites researched and the main methodologies, as well as the result found.

The presence of flavonoids confers many of the actions that are observed in the plant, and this also varies according to the conjugation or not of the metabolite with sugar, where the first increases the absorption of the molecule [11], which occurs in the intestine thinner. Flavonoids are important for the anti-diabetic, antiviral,

anti-inflammatory, anti-inflammatory, antitumor activities on capillary and hormonal permeability [12-15].

	Phytochemical
Chemical group	Method
Alkaloids	Bourchardat
	Mayer
	Dragendoff
	Silica-tungstic acid
Steroids	Gelatine
Tannins	$FeCl_3$
	Magnesium tape
Flavonoids	Fluorescence
Saponins	foam

Table 1: Phytochemical identification of the hydroalcoholic extract of *Cissus siyoicoides*.

Source: Dias., *et al*. [8].

Antidiabetic effect

Diabetes is characterized by the inactivity of insulin. Its causes major public health problems and increases the incidence of death. The increase in the number of patients and the several failures in the therapy make it possible to look for alternative sources such as plants that have a blood glucose lowering effect, such as *Cissus sicyoides*.

A study by Santos., *et al.* [16], showed that when extracts from *Cissus* is administered to diabetic patients, their blood glucose levels reduced and did not increase hormone insulin secretion. Since this plant is mainly used for type 2 diabetes, its proposed mechanism corroborates what is seen in literature for treatment. This is the decrease in glucose without increase in secretion of the hormone and thus, favoring the consumption of that quantity [17]. In addition, other pre-clinical studies have been performed, showing that the mechanism of this plant resembles that presented by the class of antidiabetic biguanides [18,19].

According to Pepato., *et al*. [18], the use of extract from Cissus in diabetic rats showed an improvement in their condition, but there was no change in the levels when the same extract was used on healthy rats. In addition, blood glucose, urine glucose and urea levels were also reduced compared to the control group. Moreover, several studies were flawed when different decoction methodologies were used, which shows that extraction is a critical factor for the antidiabetic effect to be established. The presence of glycosylated coumarins was also beneficial [6], and there was no evidence of plant-related toxic activity, and this may be one of the explanations for its wide popular use.

Anxiolytic effect

A study by Almeida., *et al*. [20] showed that plant tea use with its aerial leaves did not promote any toxicity and also did not promote any undesirable behavior or different psychological activity. In addition, the anticonvulsant effects of the plant were also demonstrated when using models with a standard anticonvulsant (Diazepan) as a positive control, and satisfactory results were obtained. The justification of anxiolytic and anticonvulsive effects of the authors corroborates other findings in literature, such as flavonoids, linalool, and α-tocopherol as the main factors responsible for this activity [21,22].

Drug administration by the intraperitoneal route suggests an interaction between the compounds found in the plant and the drugs administered, such as phenobarbital, as it is also seen in other plants, such as *Smilax* sp. [23]. Inhibition of cytochrome P450 enzymes by plant compounds appears to be primarily responsible for the increased action of anticonvulsive drugs, such as phenobarbital and *Cissus sicyoides*, producing protection against convulsions in study mice [20]. In addition, linalool also interacts with the GABA receptor, performing a modulation, as is also seen for drugs, which also affirms the anticonvulsive effect of the plant [21], and α-tocopherol has also been reported as having the same action in several plants that showed anticonvulsive potential [24].

Anti-inflammatory effect

Beserra., *et al*. [25] studied the anti-inflammatory action of the plant by administering the oral extract to rats that underwent an acute model of edema caused by xylene, while its mechanisms were evaluated by means of the involvement of the arachidonic acid and prostaglandin E2 mediators. Xylene, in these models, acts as a mediator of inflammatory characteristics such as pain, heat, redness and swelling [26], in a neurogenic way, and its evaluation was based on the characteristics of this edema that was generated in the ear.

The administration of different concentrations of the extract promoted the remission of the induced edema, and this remission was not dose-dependent, but all were satisfactory when compared to the control group, which used dexamethasone [25]. This already corroborates previous results of the anti-inflammatory action of the plant, using topical action, where the wound remission of the model was 50% in relation to the control group, but also reported problems in the topical absorption of the extract once there are a large number of components, and it was also seen the reduction of

myeloperoxidase levels in the final homogenate, and suggests that the action is also due to the accumulation of neutrophils in the area.

The action of the plant, again, is also characterized by the presence of flavonoids, which act as antioxidants and free radical scavengers, and with this, contribute greatly to the oxidative stress that is caused. In addition, the mechanism is also related to the reduction of PGE2 levels, since several authors have reported several compounds present in the plant that justify this action, such as β-sitosterol, which is one of the main components found in the plant [27] and also resveratrol [28], which has high relation with the inhibition of cyclooxygenase and also of leukotriene.

Anti-diarrhea effect

Beserra., *et al*. [25] also studied the antidiarrheal activity of the plant, using the laxative induction model of castor oil, which is metabolized in the pancreas through lipases, and generates glycerol as one of its metabolites, which is responsible for all this cascade which generates the activity [29]. The effect of the application of the extract was positive, where it acted in two ways: a decrease in the amount of liquid feces and a delay in the onset of diarrhea.

With these results, two mechanisms were proposed, where the first consisted of altered intestinal motility and delayed intestinal transit, while the second consisted of increased absorption of electrolytes and water, reducing the secretion of fluids in the gastrointestinal tract. Relationships have also been made with other antidiarrheals, such as opioids, which have a known function of reducing gastric motility and increasing electrolyte absorption [30], and for this an association of an opioid with the extract was made, and the result was negative, showing that there is no involvement of these receptors in the action of what is being studied.

We also sought to understand the involvement of α-2 adrenergic receptors, which inhibits peristaltic activity and reduce muscle tone [31], and this was done using a selective receptor agonist, where it was seen that there is no relation between this mechanism and the extract, since it was not possible to reverse the effect in the intestinal transit. Finally, the effect on the increase in traffic caused by a muscarinic agonist was tested, since intestinal transit can also be affected by mediators such as acetylcholine [32], and it was seen that the extract showed a significant decrease and states that the muscarinic receptors are involved in the reduction of peristaltic movement.

Antibacterial and antifungal activity

Beltrame., *et al*. [33] evaluated the antimicrobial activity of different fractions of the ethanolic extract of several aerial parts of the plant, using the technique of diffusion in solid agar. ATCC (American Type Culture Collection) microorganisms such as *Staphylococcus aureus* ATCC, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 15442 and *Bacillus subtilis* ATCC 6623 were used, and various antibiotics already known in literature were tested for positive control, such as chloramphenicol, vancomycin, tetracycline, and penicillin.

Two compounds, based on sitosterol, were found to be active only for *B. subtilis*, being inactivated in the presence of other microorganisms, which were already proven in the literature for other plants, such as *Vochysia divergens*, which was studied by Hess [34], where E. coli and S. aureus were resistant against a 5 mg/mL dose of the extract, while other authors have already shown the capacity of this extract against these same bacteria, plus *Salmonella typhimurium* [35]. In addition, Garcia., *et al*. [36] have already shown the effect of the extract against bacteria of the gastrointestinal tract, corroborating with the results already shown by the previously mentioned author. The antifungal activity was proven by Silva., *et al*. [37], which showed the propensity of the extract of the plant and of different fractions extracted against those causing mycotic infections, which showed that different molecules, such as resveratrol and bicyclogermacrene, that already had antifungal characteristic known due to their action in several other molecules, such as *Piper cernuum* and *P. regnellii* [38].

Vasoconstritor effect

García., *et al*. [39] studied the effect that the aqueous extract of the plant on muscular contraction, which presents two phases: phasic and tonic. This contraction indicates that *Cissus sicyoides* had the ability to provide calcium to the contractile elements of the cytoplasm. It was observed that in the presence of the extract in calcium, the norepinephrine has its maximum induced tension, corroborating with the idea that *Cissus sicyoides* increases the availability of intracellular calcium for contractile resistance.

For contraction induced by some agonists in the vascular smooth muscle, extracellular calcium is essential [40] and minimization of the response is done with the use of calcium antagonists. CS-induced contraction in aortic rings was inhibited by lanthanum, which is known to block calcium entry into the cell [41], suggesting that the aqueous extract of CS modifies the calcium infusion into the cell. The contraction of CS in calcium-free solutions can occur repeatedly in the same tissue, indicating that these contractions are a recycling of the Ca^{2+} intracellular activator. These results are in accordance with Bond., *et al*. [42] who showed that, under appropriate conditions, intracellular Ca^{2+} can be recycled. The diversity of smooth muscles may evoke reproducible contractions in the absence of extracellular Ca^{2+} [43]. The results indicate that when

calcium influx into the cell is blocked or absent, the CS extract can still produce contraction, activating the release of calcium from the cell's internal deposits. The results of these studies demonstrate that CS extract was able to induce contractions in the aorta of guinea pigs that are not dependent on extracellular calcium and that extracellular calcium is not essential to replenish intracellular stores.

Gastroprotector effect

According to the works of Ferreira., *et al*. [39], several doses of the extract of the plant were administered in rats, already aware of the toxicity of the plants, which are equivalent to all the effects previously described, and the presence of acute toxicity was ruled out [40]. Lesions caused by nonsteroidal anti-inflammatory drugs and problems caused by ethanol end up depleting gastric defenses, such as mucus and mucosa, which induce gastric lesions. The extract showed efficient values when compared to the control, and an even greater efficacy when the extract was administered before the injury caused by ethanol.

As some agents such as cimetidine, which are secretory, lack the pharmacological power to inhibit ethanol-induced ulcers, and this effect is observed when the agents have gastroprotective action [41]. This suggests that the plant is an agent that presents the second activity. The animals submitted to pre-treatment with the extract showed a decrease in the ulcerative index and an increase in the gastric volume, which did not interfere with the total gastric acid, which reinforces the gastroprotective potential of the plant.

Conclusion

Cissus sicyoides is a plant widely used through popular knowledge for the treatment of diabetes, even having the common name of "insulin" as well as in several other actions. Despite all the evidence and pharmacological studies carried up to date, there is no phytotherapeutic drug in commerce containing the plant in question, which would be something innovative, once this proposed tablet meets all the parameters. Due to its great pharmacological properties, it is of paramount importance for further studies with extracts of the plant for later use as coadjuvant in the therapy, adding the plant to an already known set that has its great use in phytotherapy.

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Conflict of Interest

There is no conflict of interest.

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