



Syzygium sp (Myrtaceae): Promising for Diabetes Treating?

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/EJMP/2015/14592

Editor(s):

- (1) Sanjib Ray, Department of Zoology, The University of Burdwan, West-Bengal, India.
(2) Marcello Iriti, Department of Agricultural and Environmental Sciences, Milan State University, Italy.

Reviewers:

- (1) Anonymous, Canada.
(2) Anonymous, Nigeria.
(3) Anonymous, Ghana.
(4) Anonymous, Malaysia.
(5) Anonymous, India.

Complete Peer review History: <http://www.sciencedomain.org/review-history.php?iid=1020&id=13&aid=8462>

Review Article

Received 8th October 2014
Accepted 4th March 2015
Published 14th March 2015

ABSTRACT

Diabetes mellitus (DM) is a growing problem worldwide which implies a huge financial burden and issues of medical care policy. DM is rapidly emerging as a major challenge to public health and is a progressive disease and one of the leading causes of death in recent times. The most common form of diabetes is type 2 diabetes (non-insulin dependent). The treatment of type 2 diabetes is complicated by several factors inherent to the disease and the increase of postprandial hyperglycemia is a risk factor. Postprandial hyperglycemia is raised by the action of glycosidases a class of enzymes that aid in the breakdown of complex carbohydrates to simple sugars such as maltose and glucose. Glucosidase inhibitors, such as α -amylase and α -glucosidase inhibitors play important roles in the treatment of hyperglycemia in diabetic patients. These inhibitors prevent or reduce the action of the enzyme α -amylase, which leads to a reduction in starch hydrolysis, showing a beneficial effect on glycemic control in diabetics. Thus, appears as a promising field, the

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search for alternative therapies such as amylase inhibitors found in natural sources such as plants. In Brazil, *Syzygium* sp was included by the Ministry of Health, in National List of Medicinal Plants of Interest to SUS (RENISUS), whose purpose is to guide studies and research that can support the development of the list of medicinal plants and herbal medicines to be made available for use population, with safety and efficacy for the treatment of most common diseases in the country. With specific regard to its hypoglycemic effect and potential use in the treatment of diabetes there are many indications suggesting such pharmacological actions.

Keywords: *Syzygium*; diabetes; amylase inhibition.

1. LITERATURE REVIEW

1.1 Diabetes

The term *Diabetes mellitus* (DM) applies to a group of chronic disorders characterized by abnormal carbohydrate metabolism. This situation stems from the lack of insulin or its inability to exert its effects. As a result, the individual with DM presents chronic hyperglycemia and possible development in the long term, micro and macrovascular complications, such as those affecting the vascular system, nerves, eyes and kidneys, leading to disease peripheral vascular nephropathy, neuropathy, retinopathy, morbidity and/ or mortality [1,2].

DM is a growing problem worldwide which implies a huge financial burden and issues of medical care policy [2]. It is a chronic disease increasingly present, affecting approximately 171 million individuals worldwide and are projected to reach 366 million people by the year in 2030 [2]. Diabetes is rapidly emerging as a major challenge to public health and is a progressive disease and one of the leading causes of death in recent times [3]. There is a great economic impact on nations. In the United States, for example, the direct and indirect costs of illness in 2007 reached 174 billion a year. In Latin America and the Caribbean in 2000 were \$ 65 billion [4]. The most common form of diabetes is type 2 diabetes (non-insulin dependent). The treatment of type 2 diabetes is complicated by several factors inherent to the disease, and the increase of postprandial hyperglycemia is a risk factor. Postprandial hyperglycemia is raised by the action of glycosidases a class of enzymes that aid in the breakdown of complex carbohydrates to simple sugars such as maltose and glucose. Glucosidase inhibitors, inhibitors such as α -amylase play an important role in the treatment of hyperglycemia in diabetic patients. These inhibitors prevent or reduce the action of the enzyme α -amylase, which leads to a reduction in

starch hydrolysis, showing a beneficial effect on glycemic control in diabetics. Glycosidase inhibitors conventionally used in the treatment of diabetes are acarbose and miglitol that competitively and reversibly inhibit the glycosidase enzyme of the intestine and the pancreas. However, these drugs are known to be associated with gastrointestinal side effects such as abdominal pain, flatulence and diarrhea [3]. Thus, a promising alternative is the detection of amylase inhibitors from natural sources such as plants.

According to the World Health Organization (WHO, 2002), up to 90% of the population of developing countries uses plants and their products, such as traditional medicine for primary health care. The WHO has listed about 800 plants that were reported as showing a potential antidiabetic agent, such as *Ficus religiosa*, *Syzygium cumini*, *Momordica charantia*, *Ocimum sanctum*, *Pterocarpus marsupium*, *Trigonella foenum-graecum* and *Allium sativum*. A great number of active principles of vegetable origin, which represent various bioactive compounds demonstrated a role for possible use in the treatment of diabetes [2].

According to information from the Unified Health System (SUS) in Brazil, DM appears as the sixth primary cause of hospitalizations and contributes significantly (30% -50%) to other causes of hospitalization, such as ischemic heart disease, heart failure, gallbladder disease, stroke and hypertension. Reduce the impact of DM means reducing the incidence of the disease, in anticipation of his appearance with preventive measures, especially in high-risk individuals [4]. The DM treatment includes, among other strategies: Education, changes in lifestyle, eating habits and readjustment of the medication, if needed. Drug treatment has two different modes: insulin therapy and therapy with oral antidiabetics. New therapeutic groups as thiazolidinediones, α -glucosidase inhibitors, third generation sulfonylureas, metformin and insulin

analogues with ultra fast action are available, allowing more consistent and logical option with pathophysiological mechanism of the disease [5,6]. Moreover, despite the wide availability of treatment options - generally a high cost to the patient - the difficulty of access to medical treatment and long tradition in the use of plant population, results in the use of alternative therapies such as herbal [5,6].

1.2 *Syzygium* sp

1.2.1 Taxonomic information

The Jambolão (*Syzygium cumini*, synonyms: *Eugenia jambolana* or *Syzygium jambolanum*) is a plant of the *Myrtaceae*, also known popularly as family Jamelão cherry Jalam, kambol, jambu, jambul, olive-the-northeast, plum-purple, olive myrtle berry-of-nun, Guape, jambuí and olive-the-land, among other names. The family comprises more than 4,620 species grouped into 129 genres. The tree is large and can reach 8-15 feet tall (Fig. 1), has a gray-brown, exfoliating and thick bark of woody scales. The wood is whitish, granular, durable, and offers brown dyes. It is described as a tree spanning about 10m in height and from 3 to 4.5 m diameter canopy projection, with abundant foliage, branches light gray coloring, with dark cracks and leaf scars quite apparent [7].

The leaves are leathery, oblong-ovate to elliptic or obovate-elliptical with 6-12 inches long (extremely variable in shape, smooth and shiny with several nerves that connect within the margin), the tip is wide and less acuminate. The fruits have coloration, initially white, becomes red and then black when ripe. They are berries and often are, oblong, 1.5 to 3.5 inches long, luscious, fleshy and edible, containing a single large seed. It has a very sweet flavor, turning slightly astringent on the edges of cellulose when it becomes mature [8,9].

1.3 Distribution

The plant was introduced in many tropical regions such as east and west of India and Africa as well as Brazil, being found in various states of the southeast, northeast and north regions [11]. Is also found in some subtropical regions such as Florida, California, Israel and Algeria [7,12]. In Brazil, this plant is found mostly in the coastal plains, in the mountains and plateaus, and grows very well in various soil types [13].

1.4 History

Historically, Jambolão was exclusive of the Indian subcontinent, but is now found growing all over the Asian subcontinent, East Africa, South Africa, Madagascar, and in the warmer regions of the United States, in states such as Florida [14]. Several species have been proposed in recent years as having hypoglycemic potential. However, *Syzygium* sp gained a prominent role, particularly in Western Europe, from the three decades before the discovery of insulin [15]. While in most cases, there are only indications of the antidiabetic properties of traditionally used medicinal plants, *S. cumini*, has been extensively studied since the late nineteenth century, after having been imported from the West Indies to Europe. The plant is traditionally used in India as an astringent and antidiarrheal. On the other hand, as an antidiabetic agent was introduced in Western medicine in 1880 [16]. Earlier from 1960 to 1970, some preliminary reports on the antidiabetic activity of different parts of Jambolão in diabetic animals were reported [9].

Throughout the twentieth century, *Syzygium* sp was widely used as a medicinal plant [17,18]. Currently, different parts of the plant Jambolão are reported in the literature to possess medicinal properties. The leaves, bark, seeds, fruits, flowers and roots are widely used in folk medicine for various indications [17,18].

In Brazil, *Syzygium* sp was included by the Ministry of Health, in National List of Medicinal Plants of Interest to SUS (RENISUS). The aim is to guide studies and research of medicinal plants and herbal medicines to be made available to the population, with safety and efficacy for the treatment of most common diseases in the country [19].

2. CHEMICAL COMPOSITION

This plant has many chemical constituents. By phytochemical screening, compounds have variability in the different structures of their anatomy, and the seeds found hydrolysable tannins (gallic acid, ellagic, corilágico), quercetin, antimelina, essential oil (α and β -pinene, camphene, myrcene, limonene, ocineno cis, trans-ocineno, γ -terpinene, bornila acetate, α -copaene, α -humuleno and candineno), and glucose resinous materials; There is still moderate amounts of protein and calcium; in shells were found acetyl oleanolic acid, triterpenoids, ellagic acid, isoquercetina,

quercetin, kaempferol, myricetin, flavonoids and tannins; in leaves, which are rich in flavonoid glycosides have been found gallic acid, metilgalato, kaempferol, myricetin, ellagic acid, chlorogenic acid, quercetin and nilocitina; anthocyanidins found in fruits and raffinose, glucose, fructose, citric acid, malic acid, gallic acid; the fruits are also rich in minerals and vitamins; finally in flowers were found oleanolic acid, kaempferol, quercetin and kaempferol; in roots are rich in flavonoid glycosides. [7,12,18,9,20,21].

3. PHARMACOLOGICAL EFFECTS

The use of tea have a strong cultural appeal. In the case of plants used for diabetes, this is particularly important because antioxidants are generally water soluble [22]. The intense use of this plant in folk medicine encouraged ethnobotanical surveys and scientific research, identifying therapeutic indications due to the numerous pharmacological actions of Jambolão, as the parts used in the plant include: Hypoglycemic/anti-diabetic (leaves, bark, fruits and seeds), anti-inflammatory and diuretic (leaves and seeds), an antiseptic (peel and fruit), anticancer (fruit) [23,24,18,25,26].

With specific regard to its hypoglycemic effect and potential use in the treatment of diabetes there are many indications suggesting such pharmacological actions [27,16,28]. According to Rizvi & Mishra [2], the blood glucose lowering effect by *Syzygium* sp may be due to increased secretion of insulin by the pancreas, or by inhibiting the degradation of insulin. On this plant is also reported an effect on lipid lowering evidenced by a reduction in blood cholesterol, triglycerides and free fatty acids. This effect has been observed due to the presence of flavonoids, saponins and glycosides in the extract, decrease activity of the enzyme 3-HMG Co-A reductase inhibitor in the liver.

On the other hand, some authors found no hypoglycemic effect in samples of *Syzygium* sp, which may, however, be related to the influence of climatic factors on the synthesis of their bioactive compounds [10].

Although *Syzygium* sp, has proven to be an important nutraceutical because of its medicinal properties, there is still a need for more scientific basis before using it for the cure of diseases. Research involving in vitro models to study the

effects of its phytochemical constituents should be performed [29].

4. DIGESTIVE ENZYMES

A therapeutic approach to the treatment of diabetes is to decrease postprandial glucose by inhibiting enzymes which hydrolyze carbohydrates, such as α -amylase and α -glycosidase present in the gastrointestinal tract. The α -amylase is responsible for cleavage of carbohydrate to maltose large, and this is converted to glucose by the action of intestinal α -glycosidase. Inhibitors of these enzymes delay carbohydrate digestion, resulting in decreasing the rate of glucose absorption and consequently a reduction in postprandial plasma glucose. Inhibitors of α -amylase and α -glycosidase play an important role in the control of postprandial hyperglycemia because they inhibit the action of glucosidase and amylase enzymes, leading to a reduction of starch hydrolysis. Thus, beneficial effects on glycemic control in diabetic patients are observed [30].

Therefore, inhibitors of these enzymes present in plants offer a promising strategy for the control of hyperglycemia associated with type 2, obesity and hypertension by reducing the breakdown of starch and glucose uptake in the intestine [31].

Several studies demonstrate the effectiveness, significance and potential of the use of amylase inhibitors [32-36], in the treatment of diabetes, obesity and associated comorbidities and reinforce the need to search for new natural sources of these inhibitors.

Table 1 shows some examples of recent studies on *Syzygium* sp and its supposed potential hypoglycemic. According to tests performed by de Souza et al. [30] and Freitas et al. [37], the jambolan showed strong inhibitory activity for α -amylase (92.84% and 98%, respectively).

Tong et al. [38], reported in their studies that *Eugenia jambolana* (Jambolão) tea contains inhibitors of α -amylase powerful because of hydrolysable tannins. These compounds have demonstrated an inhibitory activity against α -amylase that was significantly stronger than acarbose. The results provide useful knowledge about the hydrolysable tannins as inhibitors of α -amylase, which could alleviate postprandial hyperglycemia in diabetic patients.

In vitro studies showed that the jambolão extract significantly inhibited α -amylase, α -glucosidase, and sucrase activities. The heat treatment of the sample resulted in a significant increase in α -amylase inhibitory activity present in the extract, whereas a small increase in inhibitory activities of α -glucosidase and sucrase were observed. These results emphasize that the inhibition of enzymes of carbohydrate hydrolysis is a mechanism by which the Jambolão exerts its hypoglycemic effect *in vivo* [14].

Schoenfelder et al. [28], in an experimental *in vivo* study with rats have shown that treatment with *S. cumini* caused a significant decrease in blood glucose in normal animals, and on the glucose levels in diabetic animals. The leaves of *S. cumini* may be a therapeutic alternative in the treatment of diabetes, since it showed hypoglycemic and hypolipidemic activity in animals with the disease and also improving the lipid profile.

Further evidence of this potential is reported by Srivastava & Chandra [21]. The pharmacological activities of *Syzygium cumini*, particularly the anti-diabetic actions are conferred by the presence of various flavonoids and alkaloids on different parts of the plant.

Pre-clinical and clinical studies suggest that different parts of the plant *S. cumini*, mainly fruits,

seeds and stem bark possess promising activity against diabetes [39].

Recently, Widharna et al. [40] demonstrated that leaves extracts of *Andrographis paniculata* and *Syzygium polyanthum* were effective in reducing blood glucose levels in diabetic rats. Moreover, the authors also observed that the extracts preserved pancreatic islets and were safe at doses up to 2000 mg / kg body weight.

Ethnopharmacological evidence supports the hypoglycaemic effect of antidiabetic and *Syzygium* sp [18,16]. However, a few early studies related to the presence of enzyme inhibitors that eventually can participate or even be responsible for the proposed effects or toxic effects [37].

Traditional systems of medicine reveal a strong history of use to support the antidiabetic action of plants. However, the reproducibility of their safety and efficacy remains questionable. Thus, future research aimed at identifying active molecules are needed to support efficacy claims. So far, investigations are scarce on the particular compounds that the antidiabetic activity of jambolan except some recent studies. Any new compound or previously isolated from jambolan can be studied for their use in diabetic treatments. More phytochemicals and clinical studies must be made on this traditional antidiabetic plant for discovery of safer drugs [39].



Fig. 1. Jambolão (*Syzygium* sp) (Vizzotto [10])

Table 1. Recent studies on the supposed hypoglycemic potential of *Syzygium* sp

Author	Type of study / Method	Results	Comments
Ayyanar et al. [39]	The analysis was made on the Jambolão through electronic literature available in PubMed with clinical and experimental studies, using the terms: Jambolão, <i>Eugenia jambolana</i> , jambolão, jamun and java plum with and without antidiabetic effect.	The pre-clinical and clinical studies suggest that analyzed different parts of the plant, especially the fruits, seeds, and husk possess promising activity against diabetes.	The authors suggest the need for further studies and analyzes to identify the active principles present in Jambolão, and thus discover safer drugs for diabetes treatment.
Baliga et al. [14]	Structured review of experimental studies. Scientific studies were analyzed as pre-clinical studies, and laboratory testing in human trials.	The results show a decrease in glucose production and an increase in their utilization and therefore useful in the prevention of diabetes complications. Studies also show that <i>Syzygium</i> sp has an effect on the antioxidant and scavenging free radicals, prevents lipid peroxidation, the cell regenerates - pancreatic β improves glucose utilization inhibits α -glucosidases and improves dyslipidemia. These activities are beneficial in reducing hyperglycemia and preventing diabetic complications.	The authors suggest that further studies should be designed to perform double-blind clinical trials with randomized large sample size and standardized extract with appropriate controls. The findings from these studies will help in understanding and validating traditional observations about the effects of <i>Syzygium jambolanum</i> .
Freitas et al. [37]	Experimental study <i>in vitro</i> . Samples of teas <i>Syzygium</i> sp were prepared by the methods of maceration, decoction and infusion. The activity of α -amylase was determined by the methodology: 50 L and 50 L sample of the enzyme will be pre incubated in water bath at 37°C. After addition of 100 L of the substrate, the mixture is incubated. The reaction was stopped by adding 200 of 3,5 dinitrosalicílico the product and read in a spectrophotometer at 540 nm.	Extracts of <i>Syzygium</i> sp showed high percentages of inhibition of amylase enzyme, suggesting a potential hypoglycemic effect thereof. Moreover, when exposed to simulated gastric fluid, there have been significant declines in percentage of the enzyme inhibition.	The authors suggest further studies to elucidate the chemical compounds present in the extracts of <i>Syzygium</i> sp.
Schoenfelder et al. [28]	Experimental study <i>in vivo</i> . Animals divided into three groups: Normal rats, normal rats with glucose and alloxan-induced diabetic rats curve. The hypolipidemic effect was evaluated in diabetic rats induced by alloxan. This effect was compared with glyburide (medicine).	<i>S. cumini</i> treatment caused a decrease in blood glucose in normal animals (250 mg/kg - Group II) and on the levels of glucose in diabetic animals. The sheets <i>S. cumini</i> may be a therapeutic option in the treatment of diabetes as hypoglycemic and hypolipidemic which showed activity in animals with disease as well as improving the lipid profile.	The authors suggest further studies to investigate the anti-diabetic effect in humans <i>Syzygium cumini</i> .
Souza, [30]	Experimental study <i>in vitro</i> . The inhibition assay of α -amylase α was performed using a literature method, with modifications. Thirteen species of	<i>Eugenia jambolana</i> : It has been previously demonstrated to produce a strong inhibitory activity of α -amylase (98%). Subsequently, betulinic acid and tetra-flavanone have	The aim of this study was to provide <i>in vitro</i> evidence for potential inhibitors of α -amylase and α -glucosidase to generate strong

Author	Type of study / Method	Results	Comments
	cerrado plants were selected for investigation, and 39 extracts were tested for inhibitory activity of α -amylase and α - glucosidase.	been identified as active compounds.	biochemical rationale for further research in vivo and useful in diabetes clinical trials.
Srivastava & Chandra, [21]	Literature Review.	The pharmacological activities of <i>Syzygium cumini</i> , particularly the anti-diabetic actions are conferred by the presence of various flavonoids and alkaloids on different parts of the plant.	More studies should be done to detail the enzymatic mechanisms and explore the different parts of this plant in humans.
Tong et al. [38]	Experimental study <i>in vitro</i> . Kinetic studies were carried out on models in vitro digestion with the incorporation of real foods to evaluate the inhibitory effect of the amylase of <i>Eugenia jambolana</i> tea.	The hydrolyzable tannins in the tea Jambolão demonstrated an inhibitory activity against α - amylase that was significantly stronger than acarbose. These results provide useful knowledge about the hydrolysable tannins as amylase inhibitors which could alleviate postprandial hyperglycemia in diabetic patients.	The authors emphasize the importance of further in vivo studies to assess the effects of hydrolysable tannins in reducing postprandial hyperglycemia in diabetic patients.
Widharna et al. [40]	Biological assay with diabetic rats. The animals were divided into a control group and groups treated with leaves extracts of <i>Andrographis paniculata</i> and <i>Syzygium polyanthum</i> . Were evaluated: Blood glucose levels and acute toxicity.	Leaves extracts of <i>Andrographis paniculata</i> and <i>Syzygium polyanthum</i> were effective in reducing blood glucose levels in diabetic rats. Moreover, the extracts preserved pancreatic islets and were safe at doses up to 2000 mg/kg body weight.	The authors suggest that studies in human beings for the management of diabetes type II should be performed in the future.

5. CONCLUSION

Syzygium sp has great potential for use as an adjunct in the treatment of diabetes mellitus. Studies aiming the isolation of active compounds, quantification, and evaluation *in vivo* are essential to elucidate its possible mechanism of action and therapeutic application.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

We are grateful to FAPEMIG for financial support in the form of scientific initiation scholarship (BIC/Fapemig).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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