

## Popular Brazilian medicinal plants for therapeutic use in combat- ing Diabetes

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### SUMMARY

**Introduction:** Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by persistent hyperglycemia. This condition is associated with a range of complications, including cardiovascular disease, nephropathy, and neuropathy, all of which arise due to the dysregulation of glucose and lipid metabolism. Plant-derived compounds have emerged as a promising source of novel therapeutic agents for the management of T2D. Their action dwells mainly in three key mechanisms: reduction of blood glucose levels, modulation of inflammation, and attenuation of lipid mobilization. Among the active constituents identified in various plant species, compounds such as terpenes, flavonoids, alkaloids, and phenolic acids have been recognized as important candidates for mitigating mechanisms that result in diabetic complications. However, many plant species, particularly those native to tropical regions such as Brazil, remain insufficiently studied, limiting the full exploration of their therapeutic potential. **Objectives:** This review highlights five Brazilian plant species that have demonstrated traditional use in the treatment of T2D: *Sphagneticola trilobata* (L.) Pruski Astereaceae, *Salvia officinalis* Linneaus Lamiaceae, *Myrcia sphaerocarpa* DC Myrtaceae, *Eugenia jambolana* Lam., Myrtaceae, and *Bauhinia forficata* Link Fabaceae, as well as the compounds that might be responsible for their beneficial effects. **Conclusion:** Traditional Brazilian medicinal plants have been shown to exhibit a hypoglycemic effect, as well as increased insulin sensitivity, in tested animal models. Its low cost makes it an interesting research topic for Diabetes treatment.

**Keywords:** Brazilian plants; diabetes; traditional medicine; alternative therapies.

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### RESUMEN

#### Plantas medicinales brasileñas populares para uso terapéutico en la diabetes

**Introducción:** La diabetes tipo 2 (DT2) es un trastorno metabólico crónico caracterizado por hiperglucemia persistente. Esta afección se asocia con diversas complicaciones, como enfermedades cardiovasculares, nefropatía y neuropatía, afecciones que surgen debido a la desregulación del metabolismo de

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la glucosa y los lípidos. Se ha demostrado que los compuestos derivados de plantas constituyen una fuente prometedora de nuevos agentes terapéuticos para el tratamiento de la DT2. Estos compuestos actúan mediante tres mecanismos principales: reducción de la glucemia, modulación de la inflamación y atenuación de la movilización de lípidos. Los componentes caracterizados pertenecen a las clases de flavonoides, alcaloides y ácidos fenólicos, y son candidatos potenciales para el tratamiento de las complicaciones de la diabetes. Sin embargo, varias especies de plantas, en particular las nativas de regiones tropicales como Brasil, han sido poco estudiadas. **Objetivos:** Esta revisión destaca cinco especies de plantas brasileñas de uso tradicional en el tratamiento de la diabetes tipo 2: *Sphagneticola trilobata* (L.) Pruski Astereaceae, *Salvia officinalis* Linneaus Laminaceae, *Myrcia sphaerocarpa* DC Myrtaceae, *Eugenia jambolana* Lam., Myrtaceae y *Bauhinia forficata* Link Fabaceae, así como sus componentes que podrían ser responsables del beneficio terapéutico. **Conclusión:** Las plantas tradicionales brasileñas mostraron un efecto hipoglucemiante y un aumento de la sensibilidad a la insulina en modelos animales evaluados. Se requieren más estudios para explorar el potencial terapéutico de estas plantas, principalmente por su bajo costo.

**Palavras chave:** Plantas brasileñas; diabetes; medicina tradicional; terapias alternativas.

## RESUMO

### Plantas medicinais brasileiras populares, para o uso terapêutico na Diabetes

Diabetes tipo 2 (DT2) é um distúrbio metabólico crônico caracterizado por hiperglicemia persistente. Essa condição é associada com uma variedade de complicações, incluindo doenças cardiovasculares, nefropatia, e neuropatia, condições que surgem por conta da desregulação da glicose e do metabolismo lipídico. Compostos derivados de plantas têm sido uma fonte promissora de novos agentes terapêuticos para o tratamento da DT2. Estes compostos atuam em 3 mecanismos principais: redução da glicemia, modulação da inflamação e atenuação da mobilização lipídica. Os componentes caracterizados são pertencentes das classes de flavonoides, alcaloides e ácidos fenólicos, são potenciais candidatos para o tratamento das complicações da diabetes. No entanto, várias espécies de plantas, particularmente nativas de regiões tropicais como o Brasil, são pouco estudadas. **Objetivos:** Essa revisão destaca cinco espécies de plantas brasileiras que possuem uso tradicional no tratamento da DT2: *Sphagneticola trilobata* (L.) Pruski Astereaceae, *Salvia officinalis* Linneaus Laminaceae, *Myrcia sphaerocarpa* DC Myrtaceae, *Eugenia jambolana* Lam., Myrtaceae e *Bauhinia forficata* Link Fabaceae, assim como seus componentes que podem ser responsáveis pelo benefício terapêutico. **Conclusão:** Plantas tradicionais brasileiras mostraram um efeito hipoglicêmico e um aumento da sensibilidade da insulina, em modelos animais testados. Mais estudos são essenciais para explorar o potencial terapêutico destas plantas, principalmente por possuírem um baixo custo.

**Palavras-chave:** Plantas brasileiras; diabetes; medicina tradicional; terapias alternativas.

## 1. INTRODUCTION

Type 2 diabetes (T2D) is a condition characterized by an excess of glucose in the bloodstream, which can lead to various diseases. The incidence and prevalence of T2D have reached high levels, causing the disease to be categorized as an epidemic. In the current scenario, it is estimated that by 2045, around 629 million people will be diabetic [1]. Moreover, the life-threatening risk of T2D does not result directly from the condition itself but rather from the complications it triggers [2]. Among them, elevated glucose levels lead to endothelial dysfunction, contributing to cardiovascular and renal diseases. Also, insulin resistance exacerbates glucose uptake inefficiency, leading to hyperglucagonemia. Increased lipid mobilization, in turn, results in hypertriglyceridemia and inflammasome activation, which drive the production of IL-

1 $\beta$  in the context of T2D [3]. A direct consequence is the synthesis of other pro-inflammatory mediators, increasing IL-6 and TNF- $\alpha$ , further amplifying inflammation.

At the molecular level, prolonged glucose exposure can lead to the formation of advanced glycation end products (AGEs), which are linked to tissue damage and chronic inflammation. Hyperglycemia also stimulates the production of reactive oxygen species (ROS), negatively affecting mitochondrial metabolism [4]. Additionally, the shift from glucose to lipid metabolism, common in advanced diabetes, increases blood concentrations of ketone bodies, byproducts of lipid breakdown, among many other affected pathways [5]. While genetic predisposition plays a significant role in the development of T2D [6], environmental factors can reduce this risk. Beyond the traditional strategies, such as limited carbohydrate intake and regular physical exercise, the use of plant compounds shows potential in modulating the metabolic and inflammatory responses associated with T2D [7].

Accordingly, many plants have been described as influencing different mechanisms of T2D [8], and represent high accessibility due to their low cost [9, 10]. However, Brazilian plants show off an immense diversity and still lack studies regarding their impact on T2D mitigation. In this sense, this review described the cellular and molecular mechanisms influenced by the five commonly used plant extracts for treating T2D in Brazil: *Sphagneticola trilobata*, *Salvia officinalis*, *Myrcia sphaerocarpa*, *Eugenia jambolana*, and *Bauhinia forficata* (Table 1), with a focus on the active compounds present in each extract.

## 2. BRAZILIAN MEDICINAL PLANTS USED IN COMBATING DIABETES

### 2.1. *Sphagneticola trilobata*

The species *Sphagneticola trilobata*, described by L. Pruski, of the Asteraceae family, is also known as *Wedelia brasiliensis* (Spreng.) S.F. Blake, or *Wedelia paludosa* DC., or even *Wedelia trilobata* A.St. -Hil, and is commonly found in various parts of the world, such as South America and Asia [11]. In Brazil, it is known as *arnica-do-brejo*, *arnica-do-mato*, *vedélia*, *mal-me-quer do brejo*, *margaridão* and *insulina* vegetal [12, 13]. The literature highlights several popular uses of *S. trilobata* due to its broad biological activity, including antioxidant, anti-inflammatory, antimicrobial, hypoglycemic, analgesic, and larvicidal activities. These biological activities are attributed to its abundance in secondary metabolites, which include phenolic compounds, flavonoids, saponins, terpenoids, diterpenes, triterpenes, sesquiterpenes, cycloterpenes, benzene derivatives, and phytosterols such as stigmasterol [14-16], mainly in the leaves [17].

Popularly, *S. trilobata* is used as a complementary treatment for diabetes, by drinking its leaves tea [18-23]. The most widely cited characteristic of *S. trilobata* in diabetes is its hypoglycemic potential [18, 23-25], although this plant can present a very long list of promising pharmacological effects, ranging from antiviral, antibacterial, and antiparasitic activity to antioxidant, anti-inflammatory, and even antitumor activity [16, 26]. It was observed that oral administration of the ethanolic extract of *Wedelia trilobata* flowers in diabetic rats for 8 weeks reduced blood glucose levels [24]. The aqueous extract from the dried and ground leaves of *S. trilobata* administered to rats with induced diabetes for 30 days also showed a reduction in blood glucose levels [27].

The first antidiabetic mechanism observed in the use of *S. trilobata* extracts is related to the inhibitory potential of the  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes. Inhibition of these enzymes results in impaired digestion of carbohydrates, which consequently reduces glucose absorption and lowers blood glucose levels [28-34]. Extracts produced from the solvents ethyl acetate,

methanol, and water obtained  $\alpha$ -amylase inhibition rates of 52.29%, 88.38%, and 63.57%, respectively [35]. The concentration of 40  $\mu\text{g.mL}^{-1}$  of the extract produced from the whole plant in different solvents resulted in inhibition of 75% of the  $\alpha$ -glucosidase enzyme [36]. Although it is not clear which compounds are responsible for the enzymatic inhibition in *S. trilobata*, the study on another plant, *Withania somnifera*, which shares the 3-hydroxycavicol 1-[rhamnosyl-(1 $\rightarrow$ 6)-glucoside], suggested that this compound is responsible for such inhibition [34]. Bioinformatic studies suggests that camelianin A, also present in the composition of *S. trilobata*, may interact directly with  $\alpha$ -glucosidase, acting as a competitor for carbohydrate binding [37].

A second mechanism of action of *S. trilobata* extracts on glucose metabolism is the possibility of influencing insulin production or sensitivity. Unfortunately, most of the studies that have tested this herbal extract have induced diabetes through streptozotocin, a compound that selectively ablates pancreatic  $\beta$ -cells [24, 27]; while very few induce diabetes through a metabolic disorder, by using high glucose or high-fat diet, which will closely resemble type 2 diabetes [38]. Here, *S. trilobata* diminished glycemia by avoiding apoptosis of  $\beta$ -pancreatic cells by the action of a compound called 3,4-dicaffeoyl-1,5-quinolactone, tested in *Pluchea indica* extracts, shared with *S. trilobata* [39]. Still focusing on compounds that are present in *S. trilobata* but were tested in other plant extracts, the action of terpenes was described to decrease glycogenolysis by the liver and muscles, which was tested in herbal extracts from *Byrsonima crassifolia* [40]. Importantly, synergic effects should be considered for the investigation regarding the mechanism of action of these compounds, which still highlights the importance of testing if the previously cited mechanisms are also found when cells or animals are exposed to diabetic conditions together with *S. trilobata* extracts.

Another mechanism influenced by *S. trilobata* extracts is related to reduced damage caused by hyperglycemia, such as inflammatory and oxidative processes. A compound called (3 $\alpha$ )-3-(tiglinoyloxy)-ent-kaur-16-en-19-oic acid (WT-29) was described as able to modulate inflammation in LPS-stimulated macrophages by decreasing iNOS and COX-2 [41], and altering the Nrf2/Nf $\kappa$ B balance [41, 42]. In addition to WT-29 decreasing cytokine production, probably the compound (+)-7-epi-Syringaresinol 4'-glucoside is contributing to this effect, being the decrease of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 is reported in experiments testing another plant that shares this compound with *S. trilobata*, the *Mitragyna speciosa* [38]. Still, the presence of *S. trilobata* extract performed an anti-proteinase activity [43], which might indicate why this extract was related to wound healing [44] and indicate its role in diminishing glucotoxicity-induced tissue damage. In animal models, *S. trilobata* ethanolic extracts performed an antioxidant role [24], while other experiments report inhibition of catalase, delta aminolevulinic acid dehydratase, and isoforms of lactate dehydrogenase [27].

## 2.2. *Salvia officinalis*

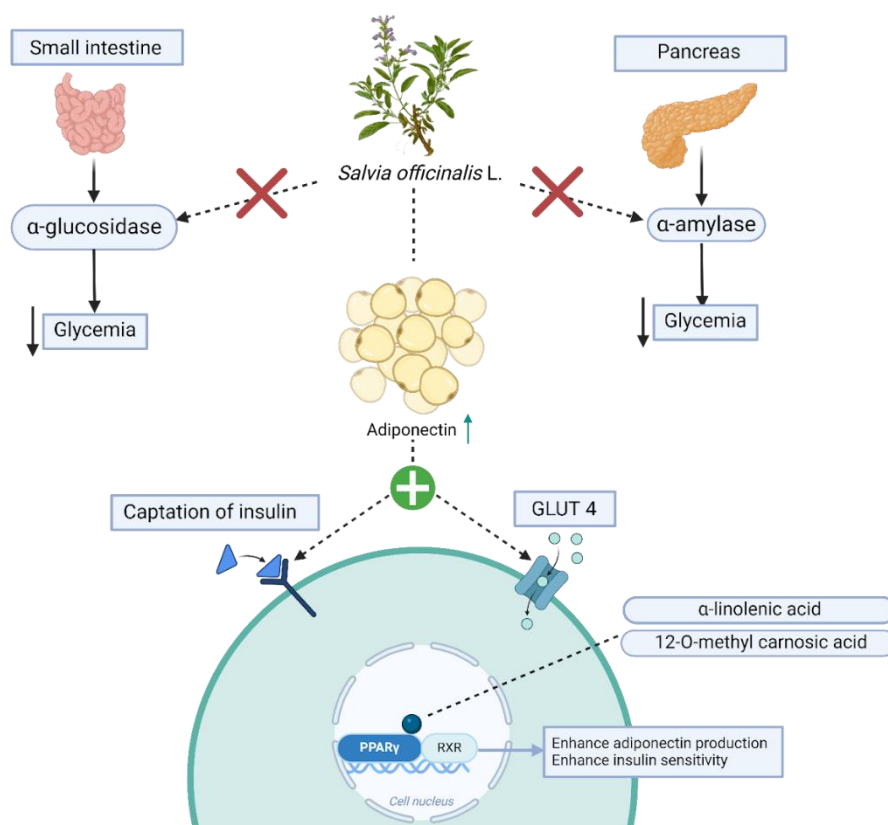
*Salvia officinalis* is a plant from the Lamiaceae family, native to the Middle East and Mediterranean regions, now is distributed worldwide [45]. The main phytochemicals extracted from the plant are primarily obtained from its flowers, leaves, and stems, presenting a diverse composition of chemical compounds with pharmacological potential [46]. Numerous extraction techniques are employed, with essential oils, alcoholic and aqueous extracts, and infusions being the most prominent [47]. The essential oil extracted from the leaves contains a high concentration of bicyclic terpenes such as  $\alpha$ -thujone,  $\beta$ -thujone, camphor, and  $\alpha$ -pinene [48, 49]. This extract has demonstrated antibacterial, antioxidant, anti-inflammatory, and hypoglycemic properties [50, 51].

Alcoholic and aqueous extracts from the leaves have resulted in high concentrations of phenolic compounds and flavonoids, as well as the presence of anthraquinones, saponins, steroids, tannins, and resins. Together, these substances have exhibited antioxidant, antifungal, anti-inflammatory, hypoglycemic, and analgesic properties [52-55]. On the other hand, infusions have demonstrated concentrations of phenolic acids, flavonoids, terpenes, hydroxybenzoic acids, and hydroxycinnamic acids [56]. These extracts have shown an antioxidative profile, enhancing GST and  $\gamma$ -GCS in mice [57]. Moreover, infusions have been found to prevent increases in body weight while decreasing total cholesterol (TC), triglycerides (TG), and LDL cholesterol (LDL-C) in mice [58].

In *in vitro* models, the sequential crude extraction of the stems and leaves of *Salvia officinalis* was assessed for its activation of the PPAR $\gamma$  pathway. It was demonstrated that different extracts, such as  $\alpha$ -linolenic acid and 12-O-methyl carnosic acid, act as PPAR $\gamma$  agonists, mainly favoring the release of adiponectin, which enhances insulin sensitivity (**Figure 1**) [59]. Furthermore, *in vitro* studies revealed that its leaves and stems extracts, obtained through decoction in a hydro-methanolic mixture, exhibited antidiabetic activity by inhibiting the enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase, which are responsible for carbohydrate digestion and monosaccharide hydrolysis, respectively [60].

*Salvia officinalis* is a plant recognized for its broad spectrum of chemical components, with antioxidant to antibacterial actions. Studies in mice have shown that oral administration of an aqueous extract of leaves increased the activity of oxidizing enzymes while reducing inflammatory mediators [61]. Additionally, its effects give the plant notable properties, especially its hypoglycemic effects in T2D individuals [62]. Several studies have shown that *Salvia officinalis* is a viable option for reducing glycemic indices in T2D models [63]. In a murine model of T2D associated with obesity, oral supplementation with an aqueous extract of leaves at two different doses (150 mg/kg and 300 mg/kg) resulted in an 8.18% and 19.16% reduction in glucose levels, respectively. In addition, insulin levels decreased by 30.88% and 49.26%, while adiponectin levels and antioxidant enzymes such as GSH and SOD increased. A reduction in inflammatory cytokines, including TNF- $\alpha$ , IL-6, and MCP-1, along with an increase in GLUT-4 expression, was also observed [64].

In humans, a randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy of *Salvia officinalis* in the treatment of T2D. The aqueous extract of leaves was concentrated, completely evaporated, and encapsulated at a dosage of 500 mg, while the placebo group received capsules containing toast powder [65]. Both groups were using metformin, glyburide, and atorvastatin in addition to the treatment with *Salvia officinalis* extract and placebo. A significant reduction in glycemic indices was observed in patients treated with the extract compared to placebo, including an 11% decrease in fasting glucose levels, a 23% decrease in postprandial glucose, and a 6.9% decrease in glycated hemoglobin [66, 67].



**Figure 1. Hypoglycemic effects of *Salvia officinalis*.** Inhibition of  $\alpha$ -glucosidase and  $\alpha$ -amylase leads to reduced glucose absorption, activation of PPAR $\gamma$ , enhanced insulin sensitivity, and increased production of adiponectin, which promotes glucose regulation and fatty acid oxidation. These pathways contribute to improved glycemic control.

In conclusion, *Salvia officinalis* exhibits a diverse profile of molecules with a wide spectrum of biological activities, ranging from anti-inflammatory to hypoglycemic effects. Its various extracts have shown similar activities, warranting further research to describe their mechanisms and potential stabilization for future treatments.

### 2.3. *Myrcia sphaerocarpa*

*Myrcia sphaerocarpa* is a shrub widely used in the treatment of diabetes by indigenous tribes in the Amazon region of Brazil. *Myrcia sphaerocarpa*, scientifically also known as *Myrcia multiflora* or *Eugenia multiflora*, has the popular name of “pedra hume caá” and is a plant species rich in phytochemicals with therapeutic potential for T2D [68]. Among the phytochemicals present in *Myrcia sphaerocarpa* extracts are flavonoids, antioxidants capable of reducing the damage caused by reactive oxygen species during cell metabolism [69]. Leaves are the parts of the plant most used for medicinal purposes, and aqueous/methanolic extracts can be produced by maceration, sonication, filtration, and infusion methods [70]. The molecular composition of *Myrcia sphaerocarpa* leaf extracts can induce hypoglycemic and antioxidant effects. The compounds that stand out are flavanone myrciacitrins I-II, the flavonols myrciacitrins, mearnsitrin, quercetin, desmantin-1, guajaverin, and the acetophenone glycoside myrciaphenone.

The glycosides are molecules whose presence in the extract also may explain the medicinal function of this plant due to their ability to inhibit aldose reductase and  $\alpha$ -glucosidase [71]. The  $\alpha$ -glucosidase enzyme is a digestive enzyme and is present in the human intestine, acting in the degradation of carbohydrates [72], producing monosaccharides that can be absorbed by

the intestine, such as glucose, fructose, and galactose [73]. By inhibiting its activity, there is a reduction in glucose uptake and post-prandial hyperglycemia [74]. Therefore, the inhibition of these enzymes from the aqueous extracts of the plant may be the main factor responsible for the therapeutic potential of *Myrcia sphaerocarpa* [75], since it exhibited more inhibitory behavior than acarbose, an intestinal alpha-glucosidase inhibitor drug [70].

Oliveira and colleagues observed that after administering dried extracts of the leaves, mice showed a 74.7% reduction in glycemic levels when compared to animals without the treatment, in a streptozocin-induced diabetes model. Long-term administration of the extract showed that the antidiabetic function was preserved, and further analysis showed a synergistic nephroprotective and hepatoprotective effect [76]. In addition to hypoglycemic effects, compounds isolated from *M. sphaerocarpa*, such as phloroacetophenone (THA), may have hypolipidemic and anti-obesity effects by reducing triglyceride absorption and inhibiting pancreatic lipase [71]. THA has effects related to increased activity of cholesterol 7 $\alpha$ -hydroxylase, a fundamental enzyme in lipid regulation by converting cholesterol into bile acid [77]. Reductions in oxidative damage related to this compound were also observed, which was able to normalize the activity of antioxidant enzymes, such as catalase, glutathione peroxidase, and superoxide dismutase in mice with oxidative liver damage induced by carbon tetrachloride (CCl<sub>4</sub>) [78].

#### 2.4. *Eugenia jambolana*

The plant known as Jamun (*Eugenia jambolana*), belonging to the Myrtaceae family and native to India, has a rich and diverse constitution. This plant is constituted by minerals, carbohydrates, and phytochemicals with broad pharmacological properties, such as flavonoids, terpenes, and anthocyanins [79]. Its fruits, which can be round, oblong, or ellipsoidal, are highly nutritious and an excellent source of sodium, calcium, phosphorus, iron, and zinc, as well as water-soluble vitamins like vitamin C, thiamine, and niacin [80]. The Jamun plant, popularly known as jambul, is recognized for its numerous properties, including antioxidant, antibacterial, and antifungal potential, as well as contributing to the supplementation of vitamins and minerals [79]. In addition to these qualities, Jamun possesses significant immunomodulatory potential, exhibiting anti-inflammatory, gastroprotective, and hypoglycemic characteristics. These aspects highlight the medical and therapeutic potential of the plant in treating various pathologies that affect many individuals [81].

The traditional use of Jamun involves processing various parts of the plant. The hydroalcoholic, aqueous, or methanolic extract of the leaves is frequently utilized for its antibacterial properties [82]. Methanolic and ethyl acetate extracts from the seeds also exhibit antibacterial activity, while aqueous, ethanolic, and acetone extracts from the bark demonstrate immunomodulatory and antibacterial effects, as well as antifungal properties [83]. Additionally, the essential oil extracted from the leaves shows a direct impact on bacteria such as *Staphylococcus aureus* and *Escherichia coli* [84].

The pharmacological effects of the plant are varied: studies show that the antioxidant potential of the pulp extract inhibited iron-induced lipid peroxidation (FeSO<sub>4</sub>) in the brain, liver, and testes of rats [85]. In addition, *Eugenia jambolana* was reported as presenting an antioxidant, metal chelating, and cytoprotective activity through chromatographic analysis, metal chelation assays, allelopathy, and cytoprotection tests both in eukaryotic and prokaryotic models. Therefore, it could be used as a new strategy against toxic metal pollution [81].

Its anti-inflammatory pharmacological potential was evidenced by the compound kaempferol-7-O- $\alpha$ -L-rhamnopyranoside isolated from the leaves, which, at doses of 3, 10, and

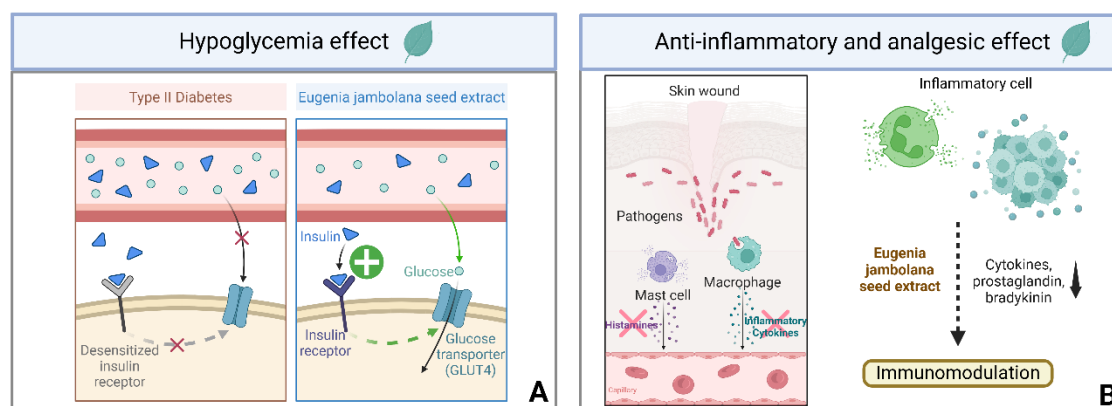
30 mg.kg<sup>-1</sup>, attenuated edema and reduced the levels of MPO, TNF- $\alpha$ , and IL-1 $\beta$  in mice with carrageenan-induced edema [86]. This compound also demonstrated significant antinociceptive effects in mice, inhibiting acetic acid-induced writhing and paw licking behavior in the formalin test, without presenting analgesic activity in central pain models. Additionally, it reduced the levels of TNF- $\alpha$  and IL-1 $\beta$  in cultures of RAW 264.7 cells stimulated with LPS, corroborating its potential as a valuable analgesic agent and supporting its use in traditional medicine for the treatment of inflammatory pain [87].

Some effects, not yet widely explored, have already been reported in the literature, i.e., Jamun extract improved diet-induced obesity, hepatic steatosis, and insulin resistance in HFD fed mice, in addition to modulating the intestinal microbiota to reduce the ratio of Firmicutes:Bacteroidetes and increase the relative abundance of beneficial genera, such as Alistipes, Prevotella, Bacteroides, Alloprevotella, and Clostridium XIVb [88]. The methanolic extract of *Eugenia jambolana* seeds demonstrated hepatoprotective effects in Wistar rats treated with carbon tetrachloride (CCl<sub>4</sub>), significantly preventing the increase in serum levels of SGOT, SGPT, ALP, ACP and bilirubin, in addition to promoting liver regeneration in a dose-dependent process, a fact that reveals its potential as a therapeutic agent for liver protection and recovery against induced toxicity [89].

*Eugenia jambolana* directly impacts glycemic levels, especially in patients with T2D. Aqueous extracts of the plant, administered to severely diabetic rabbits, resulted in a 37.1% reduction in fasting blood glucose, demonstrating a significant effect in critical conditions [90]. Furthermore, the study indicated an increase in plasma insulin levels following the administration of the seed extract, which may be attributed to the conversion of proinsulin to insulin, presumably mediated by the functionality of pancreatic cathepsin B. The extract also demonstrated a reduction in ceruloplasmin levels in diabetic rats, promoting a decrease in circulating unbound Fe<sup>2+</sup>, resulting in reduced lipid peroxidation and attenuation of inflammatory damage and complications associated with T2D [91].

Additionally, the plant *Eugenia jambolana* exhibits important immunomodulatory properties, effectively providing therapeutic action against inflammatory and metabolic alterations. The use of the extract derived from its bark promotes a reduction in the secretion of inflammatory mediators, such as cytokines, prostaglandins, bradykinin, and others, aiding in a pro-resolutive immune response in adverse situations [92]. Therefore, *Eugenia jambolana* stands out not only for its antibacterial, antifungal, and antioxidant properties but also as a potential therapeutic agent in immune modulation, functioning as an analgesic and anti-inflammatory source (**Figure 2**). Further research is needed to fully elucidate the underlying mechanisms of these effects, establishing a solid foundation for future clinical applications.





**Figure 2. Pharmacological action of compounds present in *Eugenia jambolana* extract.** *Eugenia jambolana* exhibits multiple therapeutic effects, as illustrated in the figure. A) The hypoglycemic effect of the plant is emphasized, leading to increased insulin secretion and improved glucose uptake, contributing to the regulation of blood glucose levels. B) The plant shows anti-inflammatory and analgesic action, reflected in the decrease of inflammatory cytokines and the reduction of inflammatory cell presence, supporting its potential as a therapeutic agent in inflammatory conditions. Source: Biorender.

## 2.5. *Bauhinia forficata*

*Bauhinia forficata*, popularly known as “cow’s foot” due to the shape of its leaves, composed of two leaflets joined at the base [93], is a plant of the Fabaceae subfamily, whose leaves are popularly used in Brazil and Mexico for T2D treatment [94-100].

The anti-diabetic effects of the leaf extract of *B. forficata* are associated with the presence of polyphenols and flavonoids, which would contribute to the antioxidant, anti-glycation, and enzymatic inhibition capabilities observed [98, 101, 102]. The main polyphenol compounds are kaempferol derivatives, such as kaempferol-3-O-arabinoiside, kaempferol-3-O-(2-rhamnosyl) rutinoside, kaempferol-3-O-rutinoside, astragalin, and specially kaempferitrin (kaempferol-3,7-O-( $\alpha$ )-dirhamnoside) [97, 98, 101, 102]. Myrcetin and quercetin (like quercetin-3-O-(2-rhamnosyl) rutinoside and quercetin-3-O-rutinoside) derivatives are other anti-diabetes secondary metabolites found in high concentrations, where the last one results in enzymatic inhibition [96, 101-103]. In addition, it presents predominantly alkaloids, saponins, quinones, reducing sugars, and tannins, which can also contribute to the effects associated [97]. When separating the leaves fractions (dichloromethane, hexane, water, ethyl acetate, and n-butanol), the last two fractions (and water to some extent) have most of the phenolic, condensed tannins, and flavonoid composition, both with quercetin (like isorhamnetin-3-o-glucoside) and kaempferol derivatives. The two fractions have the best anti-diabetes activity [96]. Nevertheless, the contents of the leaf extracts can vary depending on the region. Extracts from two different regions in the south of Brazil had different flavonoid concentrations, including the kaempferitrin composition [94].

Studies involving *Bauhinia forficata* mainly use rodent models, such as rats and mice, to evaluate the therapeutic effects of the extracts. The streptozotocin (STZ)-induced diabetes model in rats is commonly used to test the hypoglycemic and antioxidant effects of the plant’s extracts [98, 104]. *Bauhinia forficata* extracts are usually administered orally in animal models, reflecting their traditional use as infusions or decoctions of the plants’ leaves [105]. Studies generally use standardized doses of the aqueous and hydroalcoholic extracts, administered daily for periods ranging from days to weeks [106].

In some cases, it is administered intraperitoneally, especially in studies that require a more direct and rapid action of the extract. The doses administered can vary, but the most common range is between 100 and 500 mg.kg<sup>-1</sup> of body weight, depending on the objective of the experiment [97, 107, 108]. Treatment with the extract results in a lower conversion rate of food intake into body weight in mice. This is associated with its predominantly polyphenol composition, which increases thermogenesis and fat oxidation. In addition, *Bauhinia forficata* leaves slowly down the development of T2D in mice. However, the extract is unable to reverse the low functional capacity of  $\beta$ -cells in these mice [98]. There are also promising results in patients with T2D. Ninety-two patients, aged between 18 and 75, were treated with *Bauhinia forficata* leaves capsules (2% flavonoids), using a placebo as a control. Those who received the capsules had lower plasma levels of fasting glucose, glycated hemoglobin, C-reactive protein, and IL-6. However, the plant used in this clinical trial did not contain kaempferitrin, due to the plant's regional origin [103].

The compounds present in *Bauhinia forficata* act differently to insulin and sulphonylurea drugs, which stimulate insulin secretion by pancreatic  $\beta$ -cells. This supports the hypothesis that this plant has substances with anti-insulin action, capable of increasing the effectiveness of residual insulin in diabetic patients [99]. The mechanism of action of the plant's extracts, widely used in the treatment of T2D, is closely linked to the inhibition of digestive enzymes, such as  $\alpha$ -amylase,  $\alpha$ -glucosidase, and lipase [96]. By inhibiting these enzymes, the plant's bioactive compounds, especially flavonoids such as quercetin, kaempferol, and isoquercetin, slow down the digestion of carbohydrates and lipids, limiting the absorption of glucose and fatty acids, which directly contributes to the control of postprandial hyperglycemia and hyperlipidemia [96, 100].

*Bauhinia forficata* has proven hypoglycemic activity in pharmacological studies, mainly due to the action of compounds such as kaempferitrin, rutin, and trigonelline. Kaempferitrin plays a central role in promoting glucose uptake in skeletal muscle by stimulating the translocation of the GLUT4 glucose transporter to the cell membrane [109]. This process is associated with the reactivation of the classic insulin transduction pathway, which not only facilitates GLUT4 translocation but also promotes the secretion of adiponectin, a protein hormone that suppresses the pathophysiological events associated with the development of T2D [105].

In addition, the activation of several insulin signaling pathways, including phosphoinositide 3-kinase (PI3K), protein kinase B (PKB), atypical protein kinase C (PKC) and the mitogen-activated protein kinase (p38 MAPK) pathway, plays a crucial role in regulating glucose uptake and glycogen synthesis in skeletal muscle and liver [109, 110]. Given the mechanism of action observed, *Bauhinia forficata* can be classified as a partial agonist of the insulin signaling pathway. Although it does not replace the action of endogenous insulin, kaempferitrin improves its function by stimulating the pathways related to glucose uptake and metabolism. This effect aids glycemic control in patients with T2D, especially those with insulin resistance, without directly competing with insulin at the receptors, but by optimizing the natural processes of glycolysis and gluconeogenesis [109].

*Bauhinia forficata* has also demonstrated immunomodulatory effects that play an important role in controlling T2D, one of the main mechanisms being its ability to reduce systemic inflammation, a common characteristic of diabetic patients, often associated with insulin resistance [105]. The bioactive compounds in *Bauhinia forficata*, such as flavonoids, can reduce the production of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1, which are known to promote inflammation, contributing to insulin resistance and the deterioration of pancreatic  $\beta$  cells [111].

The plant's anti-inflammatory potential extends to the modulation of cellular components of the immune system, such as the proliferation of T lymphocytes and the activity of enzymes involved in the arachidonic acid pathway, such as phospholipase A2, cyclooxygenase, and lipoxygenase, favoring glycemic control and combating the chronic inflammation associated with the disease [111]. Therefore, the modulation of these inflammatory mediators suggests that the plant can improve insulin sensitivity and promote more effective glycemic control, preventing the worsening of chronic inflammation associated with T2D [112]. In addition, its antioxidant compounds, such as quercetin, neutralize ROS generated by chronic hyperglycemia, protecting pancreatic  $\beta$ -cells, which are essential for insulin production, and reducing oxidative stress, a key factor in cell dysfunction and the development of complications such as neuropathies and cardiovascular diseases [99].

**Table 1.** Mechanism of action of the molecules present in medicinal plant extracts.

Plant	Chemical compound	Part obtained	Extract	Model	Route of administration	Mechanism of action	Reference
<i>Sphagneticola trilobata</i>	9 $\beta$ -hydroxy-ent-kaur-16-en-19-oic acid, Pterokaurene L3 and 3 $\alpha$ -tigloyloxy-9 $\beta$ -hydroxy-ent-kaur-16-en-19-oic acid	whole plant	high polarity solvents	<i>In vitro</i> test	addition to the reaction	$\alpha$ -glucosidase inhibitory activity	[113]
	Wedtriloside A, Wedtriloside B, and 3,4-dihydroxy-cinnamic acid	dry leaves	methanol	<i>In vitro</i> test	addition to the reaction	$\alpha$ -amylase inhibitory activity	[33]
	camelianin A	-	-	<i>In silico</i> test	bioinformatic studies	$\alpha$ -glucosidase receptor agonist in carbohydrates	[37]
<i>Salvia officinalis</i> L.	phenolic acids, flavonoids, terpenes, hydroxybenzoic acids, and hydroxycinnamic acids	leaves	aqueous	mice	oral administration	Prevent increases in body weight while decreasing total cholesterol, triglycerides, and LDL cholesterol	[52, 56, 58]

<i>Eugenia jambolana</i> Lam.	<i>Myrcia sphaerocarpa</i>	-	-	-	-	-	-	-	-
kaempferol-7-O- $\alpha$ -L-rhamnopyranoside	Flavanone myricitrins I-II, the flavonols myricitrins, quercetin, desmantine, guaijaverin and the acetone	leaves	leaves	leaves	leaves	leaves	leaves	leaves	$\alpha$ -linolenic acid and 12-O-methyl carnolic acid
leaves	leaves	aqueous	aqueous	aqueous	aqueous	aqueous	aqueous	aqueous	stem and leaves
-	-	human	human	human	human	human	human	human	aqueous
mice	-	oral administration	oral administration	oral administration	oral administration	oral administration	oral administration	oral administration	<i>In vitro</i> test
-	-	Reduction in glycemic indices, decrease in fasting glucose levels, decrease in postprandial glucose and decrease in glycosylated hemoglobin	Reduction in glycemic indices, decrease in fasting glucose levels, decrease in postprandial glucose and decrease in glycosylated hemoglobin	Reduction in glucose levels, insulin levels decreased adiponectin levels and antioxidant enzymes such as GSH and SOD increased. A reduction in inflammatory cytokines, including TNF- $\alpha$ , IL-6, and MCP-1, along with an increase in GLUT-4 expression	addition to the reaction	addition to the reaction	addition to the reaction	addition to the reaction	addition to the reaction
Attenuated edema and reduced the levels of MPO, TNF- $\alpha$ and IL-1 $\beta$	Inhibit aldose reductase and $\alpha$ -glucosidase	Reduction in glycemic indices, decrease in fasting glucose levels, decrease in postprandial glucose and decrease in glycosylated hemoglobin	Reduction in glucose levels, insulin levels decreased adiponectin levels and antioxidant enzymes such as GSH and SOD increased. A reduction in inflammatory cytokines, including TNF- $\alpha$ , IL-6, and MCP-1, along with an increase in GLUT-4 expression	Inhibiting the enzymes $\alpha$ -amylase and $\alpha$ -glucosidase, which are responsible for carbohydrate digestion and monosaccharide hydrolysis, respectively	Act as PPAR $\gamma$ agonists, mainly favoring the release of adiponectin, which enhances insulin sensitivity	Act as PPAR $\gamma$ agonists, mainly favoring the release of adiponectin, which enhances insulin sensitivity	Act as PPAR $\gamma$ agonists, mainly favoring the release of adiponectin, which enhances insulin sensitivity	Act as PPAR $\gamma$ agonists, mainly favoring the release of adiponectin, which enhances insulin sensitivity	Act as PPAR $\gamma$ agonists, mainly favoring the release of adiponectin, which enhances insulin sensitivity
[86]	[71]	[65-67]	[64]	[60]	[59]	[59]	[59]	[59]	[59]

<i>Bauhinia forficata</i> Link	quercetin	-	-	-	-	Neutralize ROS generated by chronic hyperglycemia, protecting pancreatic $\beta$ -cells	[99]
	kaempferitin, rutin and trigonelline	-	-	-	-	Promoting glucose uptake in skeletal muscle by stimulating the translocation of the GLUT4 glucose transporter to the cell membrane	[105, 109]
	flavonoids	leaves	aqueous	human	oral administration	Lower plasma levels of fasting glucose, glycated hemoglobin, C-reactive protein and IL-6	[103]
	-	seed	aqueous	rabbit, rat	-	Reduction in fasting blood glucose, increase in plasma insulin levels and reduction in ceruloplasmin levels	[90, 91]

All the plants covered in the study, defining the main molecules observed in the works cited, and their actions against T2D.

### 3. CONCLUSION

Medicinal plants stand out as alternative forms of therapy for T2D due to their accessibility and are options for regions where access to conventional medicine is precarious. Extracts obtained from plants have bioactive properties with promising potential for metabolic regulation, inflammatory and antioxidant modulation. Extracts of *Sphagneticola trilobata*, *Salvia officinalis*, *Myrcia sphaerocarpa*, *Eugenia jambolana*, and *Bauhinia forficata* have been shown to have a hypoglycemic effect in various animal models, an effect resulting from the inhibition of digestive enzymes or increased insulin sensitivity. Further studies into the effects of medicinal plant extracts on humans are necessary in order to demonstrate their efficacy and safety in therapeutic use.

The accessibility and low cost of these plants are advantages for the development of new phytotherapeutic drugs, increasing access to patients in need of public health, as well as valuing traditional knowledge. Despite the advances in the knowledge about these plants, the development of new drugs requires robust clinical studies to guarantee the efficacy and safety of medicinal plants. The present review sheds light on the field of plants that can be used in the T2D treatment. A better understanding of the plant-derived compounds could, therefore, be applied for diabetic treatment.

## STATEMENT DECLARATIONS

**Competing interest:** The authors declare that there is no conflict of interest.

**Data availability:** Data availability not applicable to the manuscript.

**Founding statement:** No foundings were received for this manuscript.

**Ethics statement:** Not applicable to the manuscript.

**Dual publication:** This manuscript is not published or under consideration elsewhere.

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