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STUDY THE MOLECULAR MECHANISM OF *SALVIA SPECIES* IN PREVENTION OF DIABETES

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ABSTRACT: Diabetes mellitus is a widespread epidemic caused by insulin deficiency, decreased secretion, or both of them. This disease is one of the common metabolic disorders that affects 8.2% of the world population and is expected to reach 4.5% in 2025. More than 200 species of plants have anti-diabetic properties, but the mechanism of their effect is not well defined. Most herbs that have anti-diabetic properties include to the family of Leguminoaceae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae and Araliaceae. The antidiabetic activities of medicinal plants are attributed to the presence of polyphenols, flavonoids, terpenoids, coumarins and other constituents which show reduction in blood glucose levels. Searching among the different literature resources and various database and in view of the above aspects, the present article provides a comprehensive review on the available antidiabetic *salvia species* that have been approved by pharmacological and clinical evaluations, and whose mechanism(s) of action is assured. Numerous mechanisms of actions have been proposed for *Salvia species* extracts. Some hypotheses relate to their effects on the activity of pancreatic beta cells, increase in the inhibitory effect against insulinase enzyme, increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may also be involved such as increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen or decrease of glycogenolysis, inhibition of intestinal glucose absorption, reduction of glycemic index of carbohydrates and reduction of the effect of glutathione.

INTRODUCTION: Diabetes mellitus is a common disorder of carbohydrate, fat, and protein metabolism, which results in high levels of glucose in the body after a meal or fasting.

This disease is caused by the absence or reduction of insulin secretion, and accordingly, diabetes is usually classified into two types, type I (insulin dependent, IDDM) and type II (non-insulin dependent, NIDDM). This division was first introduced by Avicenna in his book "The Canon of Medicine".

According to pathophysiology and intensity of this disease, it can controlled by medicinal plants, diet, exercise, various synthetic hypoglycemic agents, and / or insulin.

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Despite the identification and utilization of hypoglycemic compounds, diabetes and its complications are still a major health problem in the world. Herbal products may contain several active agents or compounds that can act in a variety of ways to bring about the effects of several biological pathways and reduce the symptoms of diabetes. As a result, multiple benefits are provided¹. However, this opinion is not entirely new, since before and after the discovery of insulin, plants have been used with hypoglycemia in folk medicine and are still prevalent². As confirmation of this issue, metformin, which is significant for the significant effect on the prevention of diabetes, was purified from the French lilac *Galega officinalis* L.; also, other reasons for using these compounds as natural medicine are low cost and minimal side effects.

More than 400 plant species represent hypoglycemic activity. Plants used to treat diabetes often affect their effects by increasing insulin secretion, increasing glucose uptake by skeletal muscle and fat tissues, inhibiting liver glucose production and inhibiting intestinal absorption of glucose. The main active components of diabetes are terpenoids, alkaloids, glycosides, steroids, carbohydrates, glycopeptides, amino acids and mineral ions. *Salvia species* has about 900 species in the world, including several medicinal, ornamental and culinary species.

Approximately 58 species of *Salvia* have been known in Iran, including *S. mirzayanii*, *S. eremophila*, *S. macrosiphon* and *S. sahendica* as endemic species³. *Salvia species* are used throughout the world in traditional medicine and are active in terms of medicine, because of their insecticidal⁴, antifungal, antioxidant⁵, anti-diabetes, anticholinesterase and memory enhancement of patients with Alzheimer's disease⁶ activities. *Salvia species* are rich sources of phenolic acids and flavonoids and quercetin.

Flavonoids, in particular, have a positive effect on diabetes, by acting an inhibitory effect on the aldose reductase enzyme that may play a role in the complications of diabetes⁷. Quercetin reduces glucose and increases plasma insulin levels in STZ-induced diabetic rats⁸. Since glucose hemostasis is affected by several cases, in the current review, the hypoglycemic effects of *Salvia species* and molecular mechanisms of reduction blood glucose were studied separately. Different search engines were explored including Pubmed, Google, Asc database by using different keywords. The effectiveness of the hypoglycemic *Salvia species* is obtained by inhibiting the absorption of glucose from the intestine, increasing insulin secretion from the pancreas, inhibiting the production of glucose from hepatocytes, or increasing glucose uptake in peripheral tissues through glucose transporters **Fig. 1**.

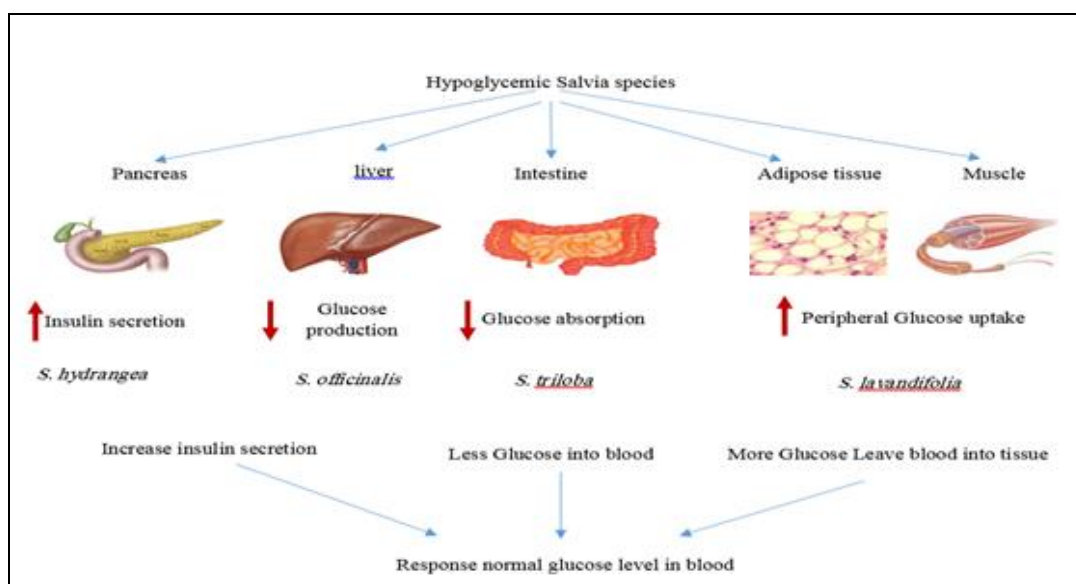


FIG. 1: HYPOGLYCEMIC MECHANISM OF SOME SALVIA SPECIES AND EFFECT ON TARGET TISSUES

Insulin Secretion: Under normal circumstances, the beta cells of the Langerhans Islands secrete

enough insulin to maintain blood-balance levels in the range 72-126 mg/dL **Fig. 2**⁹.

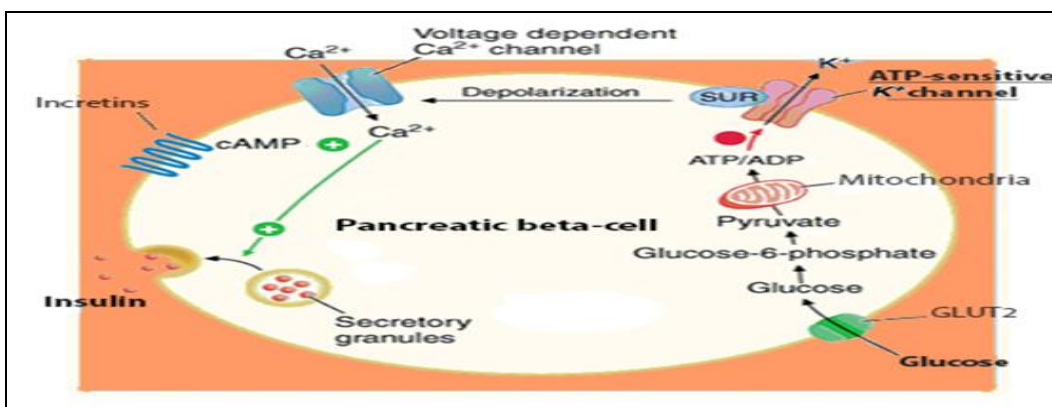


FIG. 2: GLUCOSE ENTRY TO BETA CELLS BY GLUCOSE TRANSPORTER GLUT2 AND PHOSPHORYLATION TO GLUCOSE-6 PHOSPHATE AND INCREASED ATP BY GLUCOSE METABOLISM IN THE CYTOPLASM, POTASSIUM CHANNEL KATP CHANNELS, LEADING TO CELL MEMBRANE DEPOLARIZATION AND SUBSEQUENTLY OPENING VOLTAGE-GATED Ca^{2+} CHANNELS. THESE CHANGES INCREASE FREE Ca^{2+} CONCENTRATION IN CYTOPLASM AND EVENTUALLY TRIGGERS INSULIN SECRETION ¹⁰

Glucose Transporters and Insulin Signaling Pathway:

Factors that stimulate the absorption of peripheral blood glucose and control blood levels have different mechanisms. These factors control blood sugar in patients with type 2 diabetes. The activation of GLUT-2 in the liver, GLUT-4 in skeletal muscle and adipose tissue, increasing the release of positive adipocytokines, such as adiponectins as well as induction of the nuclear receptors, PPARs, especially the gamma subtype accelerate glucose uptake process. GLUT-2 is found in the liver, pancreatic β -cells, kidney and small intestine. Low-affinity GLUT-2 has a role in detecting glucose concentrations in the islets of Langerhans. Whereas GLUT-4 is present in skeletal muscles, adipose tissue and the cardiac muscles.

Of all the GLUT, only GLUT-4 is insulin-responsive. GLUT-4 is stimulated by the secretion of insulin and moves towards the plasma membrane. Thus, reducing GLUT-4 mRNA gene expression reduces glucose uptake by insulin ¹¹; therefore, imperfect GLUT4 function could be a causative factor for insulin resistance ¹². With regard to the above, the plants and effective compounds that present in them which increase the GLUT-4 expression are more effective in accelerating the translocation of this transporter and are effective in treating insulin resistance and hyperglycemia. The insulin stimulation followed by cascade signaling enhances glucose intake, utilization and storage in various tissues **Fig. 3.** ¹³.

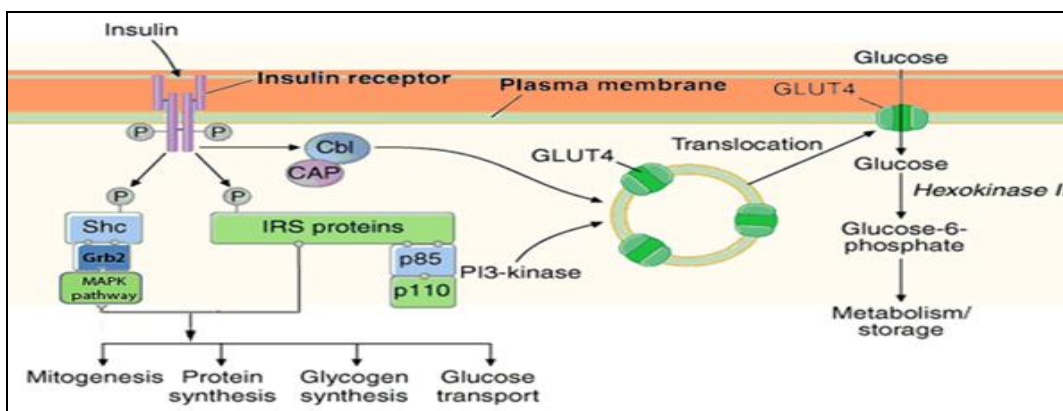


FIG. 3: INSULIN SIGNALING PATHWAY AND INSULIN INSENSITIVE. THE INNER PART OF INSULIN RECEPTOR IR REVEALS A TYROSINE KINASE ACTIVITY AND COUPLED WITH MULTIFUNCTIONAL DOCKING PROTEINS IRS-1 AND IRS-2. THE IN TURN SIGNALING LEADS TO AN ACTIVATION OF THE MAPK CASCADE INVOLVED IN MITOGENESIS AND THE OPEN STATUS OF A HEXOSE TRANSPORTER PROTEIN GLUTS WHICH IS LOCATED IN THE CELL MEMBRANE AND IS THE ONLY CHANNEL FOR GLUCOSE ENTRY INTO CELLS. THE DECREASED SERINE/THREONINE PHOSPHORYLATION OF IR, INACTIVATES HEXOKINASE AND GLYCOGEN SYNTHASE, AS WELL AS DEFECTS IN THE PHOSPHORYLATION OF GLUCOSE TRANSPORTER PROTEIN GLUT4 AND GENETIC PRIMARY DEFECT IN MITOCHONDRIAL FATTY ACID OXIDATION, LEADING TO INSULIN RESISTANCE AND AN INCREASE OF TRIGLYCERIDE SYNTHESIS CONTRIBUTE TO THIS INSULIN IN SENSITIVITY ¹⁴

Salvia Species used to treat Diabetes:

Salvia lavandifolia: *Salvia lavandifolia* is a member of Lamiaceae family. Hypoglycemic effect of *Salvia lavandifolia* may be due to potential of insulin release induced by glucose. In case of chronic treatment, hyperplasia of pancreatic islet beta cells was suggested to act as physiological background for the hypoglycemic activity of the *S. lavandulifolia* aqueous extract. The antidiabetic activity of *Salvia lavandifolia* extract at 10 mg/kg induced an increase in the size and number of the cells in the islets of Langerhans with increase in pancreatic insulin content¹⁵. Treated with *S. lavandulifolia* aqueous extract indicate that hypoglycemic action may be a result of several synchronous mechanisms. Hypoglycemic effect of *Salvia lavandifolia* may arise by several mechanisms such as: a potentiation of insulin release induced by glucose; b increased peripheral uptake of glucose; c decreased intestinal absorption of glucose; and d) hyperplasia of the pancreatic islet beta cells. *Salvia lavandulifolia* are used in the treatment of diabetes mellitus in Spain. Jamenez et al., studied its effect and reported its hypoglycemic activity in normal as well as alloxan diabetic rabbits. The hypoglycemic effect is slight and independent of effects of insulin¹⁶.

(Jimenez et al., 1990) have been investigated the effect of *S. lavandifolia* extract on STZ-induced diabetic rats. The results show that the extract 10 mg dry residue/kg) induced an increase in the size and number of cells in the islets of Langerhans. There was also an increase in pancreatic insulin content. A significant decrease (>40%) in blood glucose levels was obtained when the extract (10 mg/kg) and glibenclamide (1 mg/kg) were both administered to STZ-induced diabetic rats¹⁵.

Salvia officinalis: *Salvia officinalis* tea reduces fasting plasma glucose level in mice and also inhibits gluconeogenesis and glycogenolysis in the liver. Hepatocyte glucose production in rat cells under the influence of this *Salvia* tea is low in comparison with the control group. Glucagon did not increase gluconeogenesis in animal cells that are under the influence of *Salvia officinalis* tea drinking. Although *Salvia* tea is not like the effect of metformin, it decreases gluconeogenesis in hepatocytes as well as hepatocytes response to insulin increasing by *Salvia* tea.

Although the authors stated that insulin might have facilitated the hypoglycemic effect of the extract, by doing experiments on animals fasting, it is observed that consumption of *Salvia* tea inhibits the gluconeogenesis¹³.

In STZ-treated rats, insulin deficiency increases gluconeogenesis through enhanced lactate and pyruvate uptake and flux through the enzyme Phosphoenolpyruvate carboxykinase (PEPCK). Metformin has been shown to reduce substrate flux through this enzyme and inhibit PEPCK gene expression, thereby decreasing gluconeogenesis. This inhibition of gene expression seems to occur mainly through an insulin-independent pathway¹⁷. This agrees with the possibility that sage (*Salvia*) tea and/or sage essential oil requires an intact insulin signaling pathway to produce its effects which were observed only in normal rats. Results with laboratory rats shown that essential oil (1950 mg/kg, i.p.) in *S. officinalis* proved to be hypoglycemic active in normal or in alloxan-induced diabetic rats.

Eidi et al., in 2005 showed that the methanol extract of *S. officinalis* causes a significant reduction in glucose concentrations on STZ-induced hyperglycemic rats but does not affect healthy fasting rats. The researchers have found that the use of essential oils in *Salvia officinalis* did not change in serum glucose levels¹³.

In another study, the effect of *Salvia* on reducing blood glucose, glycosylated hemoglobin (HbA1c), lipid profile, liver and kidney function tests has been studied. A double-blind clinical trial was carried out on 80 type II diabetic patients who had not reached the ideal control of the disease. Patients were randomly divided into two equal groups of case and control. The case group received *Salvia officinalis* and the control group received placebo tablets three times a day for three months. The fasting blood sugar (FBS) and 2 h postprandial (2 h pp) glucose were checked at the beginning and every 2 weeks, for three months. Results showed that the 2 h pp blood sugar and cholesterol levels significantly decreased in *Salvia-officinalis* treated patients compared to the control group ($p < 0.05$). There were no significant changes in HbA1c and FBS between the two groups¹⁸.

In another research antidiabetic effect of methanol extracts of the sativum (Garlic), *A. ascalonicum* (Persian shallot), and *S. officinalis* (Sage) on alloxan diabetic rats was investigated. After 3 weeks of treatment by methanol plant extracts, increased expression of insulin and GLUT4 gene in diabetic rats treated with these plants extracts was observed.

S. officinalis reduces blood glucose like acarbose, and also inhibits the activity of the intestinal maltase and sucrase enzymes and therefore has antidiabetic activity¹⁹.

The effect of aqueous and ethanol extracts of *Salvia officinalis* leaves at concentration (100 mg/kg) in dosage on albino rats for 14 days, on blood glucose, serum cholesterol and triglycerides TG level in induced-diabetic rats by alloxan (150 mg/kg) compared with the reference drug Glibenclamide. Also, an evaluation of the active commercially available sage oil was analyzed by TLC. Results showed significant reduction ($P < 0.05$) of fasting blood glucose level in alloxan-induced diabetic rats treatment with plant extracts and glibenclamide drug as compared with infected control group. And the sage leaves extracts gave a good results, even better than glibenclamid drug for lowering blood sugar. Also, the results showed a significant increase ($P < 0.05$) in cholesterol levels compared to healthy control group as well as a significant decrease ($P < 0.05$) in the level of TG of diabetic rats when treatment with aqueous and alcoholic extract of the plant leaves in comparison with the healthy control group²⁰.

***Salvia hydrangea*:** In alloxan or STZ-induced diabetic rats, increase blood glucose levels indirectly increase the levels of cholesterol, TG and LDL²¹. Increased cholesterol levels in diabetic rats resulted in decreased insulin levels and reduced fat storage in the liver that can cause hyperlipidemia and elevated plasma cholesterol increase in Blood glucose concentrations in diabetic rats reduced the amount of insulin and its effects. Lack of insulin leads to increased lipolysis in adipose tissue and fatty acids in the liver²². Consumption of alcoholic extract of *S. hydrangea* caused an increase in insulin, HDL levels and decrease blood cholesterol and glucose levels²³. Alpha-amylase is an important enzyme in humans that breaks down

starch into simple sugars. Inhibition of this enzyme inhibits carbohydrate digestion and absorption of glucose. The activity of this enzyme is reduced by different species of *Salvia* such as hydrangea²⁴. *Salvia hydrangea* had better antidiabetic properties than *S. lavandulifolia* and *S. fruticose*²⁵. *S. lavandulifolia* can reduce blood glucose in diabetic rabbits, while in normal animals it inhibits hyperglycemia through reducing intestinal glucose uptake. Thus, it is said to have an insulin-dependent effect. *Salvia hydrangea* can reduce blood glucose levels and decrease intestinal absorption of glucose in diabetic rats and will be no change in plasma insulin levels²⁵. Consumption of alcoholic extract of *S. hydrangea* reduced AST and ALT serum levels which may be related to decrease ATP production in the absence or deficiency of insulin.

The compounds in *Salvia hydrangea* extract have antioxidant properties that reduce oxidative stress and have hypoglycemic effects. Alcoholic extract of *Salvia hydrangea* also protects the kidney against diabetes²⁶. *S. hydrangea* has strong antioxidant properties. It also contains phenolic compounds²⁵, Polyphenolic compounds and flavonoids can also resuscitate the cells against glutathione reduction and protect them by increasing the capacity of anti-oxidant enzymes glutathione, glutathione reductase, glutathione peroxidase, and catalase²⁷. Some of flavonoids in extracts of *S. hydrangea* reduce damage to the liver and kidney²⁸.

***Salvia miltiorrhiza*:** *Salvia miltiorrhiza* often used in compound procedures for therapy of diabetic complications. A USA patent showed the aqueous extract of *Salvia miltiorrhiza* has been administered to diabetic patients for care of diabetic nephropathy. Considering the fact that *Salvia miltiorrhiza* Compositae (SMCO) significantly increased the SOD levels, it is inferred that SMCO could resist lipid peroxidation injury and be helpful for diabetic complications²⁹. The compounds in the 75% ethanol extract from roots of *Salvia miltiorrhiza* Bge. Cause α -glucosidase inhibitory effect and formation of advanced glycation end-products AGEs³⁰.

***Salvia fruticosa*:** The expression of SGLT1 in the BBM of enterocytes increases by a diet rich in carbohydrates that increase luminal glucose³¹.

Also, the level of GLUT2 increases in diabetic rats as well as in human samples with diabetes³². *S. fruticosa* inhibits the adaptive increase of SGLT1 levels in BBM of rat enterocytes after induction by STZ treatment and as a result of stimulation with high carbohydrate diet. Rosmarinic acid seems to be the active principle. In addition to the health benefits on glycemia control, *Salvia* extracts and Rosmarinic acid have recently been shown to prevent colon cancer through prevention of DNA damage, inhibition of cell proliferation and induction of apoptosis³³. Perfumi et al., reported the ability of *Salvia fruticosa* to reduce blood glucose levels in alloxan-hyperglycemic rabbits, but not in normoglycemic animals, without modifying plasma insulin levels³⁴.

***Salvia triloba*:** Water extracts of leaves of *S. triloba*, used in folk medicine of the eastern Mediterranean regions as a hypoglycemic agent. Oral dose of 0.250 g/kg body weight caused a significant reduction in blood glucose levels in alloxan-hyperglycemic rabbits, but not in normoglycemic animals. The hypoglycemic effect was induced by the single oral dose of water extract in both normoglycemic and alloxanhyperglycemic rabbits orally loaded with glucose. However, in these animals, the *S. triloba* extract did not modify plasma insulin levels. The hypoglycemic effect of the drug was not demonstrated in rabbits which received glucose load intravenously. This data suggests that *S. triloba* treatment produces hypoglycemia mainly by reducing the intestinal absorption of glucose³⁵.

***Salvia aegyptiaca*:** In a study conducted by Abdel-Zaher AO et al., in 2005, the hypoglycemic effects of 31 plants in different areas of Egypt were studied. Twenty-one plant extracts were given orally to normal rats, and fifteen were tested on fasting and alloxanized rats. The results were compared with a standard oral hypoglycemic drug DAONIL tablets also known as glyburide (USAN), a second-generation sulfonylurea antidiabetic agent used as a positive control. Eight plants exhibited persistent hypoglycemic effects, while transient hypoglycemic effects appeared in response to the administration of four other plants. Among the fifteen plant extracts tested on alloxanized diabetic rats, only four showed hypoglycemic effects more potent than those of the administered dose of

DAONIL® tablets. These were *Matthiola livida* (Delile) DC. (Brassicaceae), *S. aegyptiaca* L. (Lamiaceae), and *Arthrocnemum glaucum* Ung.-Sternb. (Chenopodiaceae). *S. aegyptiaca* also induced the hypoglycemic effect in fasting alloxanized diabetic rats³⁶.

***Salvia sahendica*:** *S. sahendica* has many different biological activities; for example, it has been used as an antimicrobial agent in Azarbayejan province of Iran. *S. sahendica* has been used as both a medicinal and culinary plant for seasoning, flavoring, and preserving foods. Due to its ability to slow oxidization in foods, it has long been used as a food preservative. Biological activities of *S. sahendica* such as antibacterial, antioxidant, antiglycation and anti-inflammatory have been reported as well. It seems that rosmarinic acid is one of the main compounds of *S. sahendica* extract that could cause this plant to be neuroprotective³. *S. sahendica* possesses strong antioxidant capacity, which was higher than the other investigated *Salvia species* endemic to Iran³⁷.

***Salvia acetabulosa*:** Methanol extract of *S. acetabulosa* revealed strong inhibitory properties against α -glucosidase and α -amylase with IC₅₀ values of 76.9 and 91.2 μ g/ml, respectively. This extract revealed the highest potency against angiotensin converting enzyme (ACE) with IC₅₀ of 52.7 μ g/ml. The total phenolic content in this extract was comparable with *Marrubium radiatum* (80 mg/g). The activity of *S. acetabulosa* n-hexane extract on both digestive enzymes was weaker, with an IC₅₀ of 205.5 and 212.0 μ g/ml for α -amylase and α -glucosidase, respectively. This extract was rich in terpenes and fatty acids. Several *Salvia species*, including *S. acetabulosa*, have been reported in Iranian folk medicine as hypoglycemic agents³⁴.

Chemical Constituents in Salvia Species: Various studies have been done to determine the chemical composition of *Salvia species* example, the important oil of *Salvia*. For *stenophylla* collected in the Free State of South Africa was investigated by GC-MS³⁸. The volatile monoterpenoids, especially α -phellandren exists with high concentrations (28% of total oil). The oxygenated monoterpenoids founded 5% of the oil, and the sesquiterpene hydrocarbons founded (35.5%).

TABLE 1: LIST OF SOME OF THE MOST POPULAR *SALVIA SPECIES* USE FOR ANTIDIABETIC PURPOSES

Species	Part of plant used/ type of extract	Experimental model	Target & antidiabetic effect	Reference
<i>S. lavandifolia</i>	Aqueous extract	STZ- induced diabetic rats	increase in pancreatic insulin content	15, 16
	Aqueous extract	Alloxan induced diabetic rats	hyperplasia of pancreatic islet beta cells	15
	Aqueous extract	STZ- induced diabetic rats	induced an increase in the size and number of the cells in the islets of Langerhans	15
	Aqueous extract	Alloxan induced diabetic rats	decreased intestinal absorption of glucose	15
	Aqueous extract	STZ- induced diabetic rats	increased peripheral uptake of glucose	16
<i>S. officinalis</i>	Leaves/ aqueous and Alcoholic extract	STZ- induced diabetic rats	inhibits gluconeogenesis and glycogenolysis in the liver	13
	Aqueous extract	Diabetic patients	inhibit PEPCK gene expression	17
	Aqueous extract	STZ- induced diabetic rats	reduction in glucose concentration	13
	Aqueous extract	Alloxan induced diabetic rats	decrease blood sugar and cholesterol levels	18
	Alcoholic extract	STZ- induced diabetic rats	increased expression of insulin and GLUT4 genes	19
	Aqueous extract	STZ- induced diabetic rats	reduce fasting blood glucose level and decrease in the level of triglyceride	20
	<i>S. hydrangea</i>	Alcoholic extract	Alloxan induced diabetic rats	increase in insulin, HDL levels and decrease blood cholesterol and glucose levels.
Alcoholic extract		Alloxan induced diabetic rats	reduce The activity of Alpha-amylase	24
Alcoholic extract		Alloxan induced diabetic rats	reduce AST and ALT serum levels reduce oxidative stress protects the kidney against diabetes	26
<i>S. miltiorrhiza</i>	Aqueous extract	Diabetic patients	increased the superoxide dismutase levels resist lipid peroxidation injury cause α - glucosidase inhibitory effect formation of advanced glycation end-products	30
<i>S. fruticosa</i>	Aqueous extract	STZ- induced diabetic rats	inhibits the adaptive increase of SGLT1 levels in BBM of rat enterocytes	31
	Aqueous extract	alloxan- hyperglycaemic rabbits	reduces blood glucose levels without modifying plasma insulin levels	34
<i>S. triloba</i>	Water extracts	Alloxan -induced diabetic rabbits	reduce the intestinal absorption of glucose	35
<i>S. acetabulosa</i>	Methanol extract	bioassay method	inhibitory properties against α -glucosidase and α - amylase	34

Between the oxygenated sesquiterpenoids which constitute the most of the oil 46%), α -bisabolol (41%) and manool (4%) were the most abundant. These compounds are generally responsible for the constant wood odour. *S. stenophylla* and *S. stenophylla* contains very low amounts of 1, 8-cineole and camphor. Fourty four combinations with the analysis of essential oil of *S. stenophylla* have been identified. The oil contained 29.8% α -bisabolol, which was isolated by column chromatography and identified as (+)-epi- α -bisabolol.

An exudate of *S. stenophylla* was inspected for flavonoids. Apigenin, apigenin-7-methyl ether, luteolin, scutellarein-7, 4'-dimethyl ether and 6-hydroxyluteolin-6, 7-dimethyl ether collected in the exudate.

S. verbenaca growing in Spain, and apigenin, luteolin, salvigenin and 5-hydroxy 7', 4'-dimethoxy flavones had been separated from its leaves³⁹. A root extract of Egyptian *S. verbenaca* plants contained taxodione, horminone and 6 α hydroxy-7 α -acetoxyroyleanone.

A large study on the occurrence of alkaloids in plants also included a number of the southern African *Salvia* species. *Salvia chamelaeagmea*, *S. namaensis* and *S. runcinata* tested positive for alkaloids, whereas *S. africanacaerulea*, *S. africanalutea*, *S. coccinea*, *S. dolomitica*, *S. reflexa*, *S. tiliifolia* and *S. triangularis* tested negative³⁵.

Aromatic plants are considered as a primary source of potential all chemicals and are toxic almost without exception. Our *in-vitro* experiments on the essential oils from *S. hierosolymitana* and *S. multicaulis* var. *simplicifolia* collected in Lebanon on germination and initial radical elongation of radish and garden cress, show that the essential oil of *S. multicaulis* var. *simplicifolia* was more active, whereas *S. hierosolymitana* oil didn't show such activity. The phytotoxic activity of *S. multicaulis* var. *simplicifolia* is probably due to the presence of a substantial amount of oxygenated terpenoids, along with the presence of α -pinene (5.5%) and *p*-cymene (2.3%)⁴⁰.

Terpenoids in the Genus of *Salvia*: Research shows that the main components of *Salvia species* are flavonoids and terpenoids⁴¹. The roots of these plants are composed of diterpenoids compounds, while the aerial parts usually contain flavonoids and triterpenoids as well as volatile compounds like monoterpenoids. American *Salvia species* have diterpenes in the aerial parts. Both sesquiterpenoids and sesterterpenes are slightly rare in *Salvia species*³⁵. Flavonoids are useful in the treatment of diabetes, for example, *Salvia* is an glycoside isorhamnetin inhibits aldose reductase enzyme that plays an important role in disorders of diabetes. Glycoside kaempferol has hypoglycemic effect and increases glucose uptake by muscle in normal rats³⁷.

DISCUSSION: Diabetes is a major metabolic disorder of carbohydrate, protein, and fat, which is due to insufficient production of insulin or because of its inhibitors. This disease causes major economic losses to countries and impedes the progress of nations⁴². Natural treatments were used before the drug was produced by pharmaceutical companies and they can still be used today. There are many plants with strong antidiabetic properties. Herbal remedies for diabetes have been used in patients with insulin dependent diabetes, noninsulin dependent diabetes, diabetic nephropathy, diabetic

retinopathy *etc.* The families of plants with the most effective hypoglycemic effects contain Araliaceae, Asteraceae, Cucurbitaceae, Euphorbiaceae Leguminoseae, Lamiaceae, Liliaceae, Moraceae, and Rosaceae. In most trials, STZ and alloxan induced diabetic mouse or rat are used to study the effects of antidiabetic plants. *Salvia* tea is used as a food or dietary supplements. The extracts of these plants are rich in antioxidants and play an important role in reducing the cost of treatment of diabetes, as well as *Salvia* tea has no toxic effects in the liver⁴³.

Salvia species have rosmarinic acid. The amount of this compound in plant extracts of various *Salvia species* is between 28 and 64 $\mu\text{g}/\text{mg}$. This compound is involved in the scavenging of free radicals⁴⁴. The antioxidant capacity of *S. sahendica* is higher than other *Salvia species* in Iran³⁷. One of the main ingredients of the *S. sahendica* extract is rosmarinic acid (67 $\mu\text{g}/\text{mg}$), which also has the neuroprotective of this plant. Meanwhile oxidative stress is a critical event in the pathogenesis of neurodegenerative diseases, its neuroprotective effects along with its antioxidant and antiglycating properties implies the possibility of using *S. sahendica* as a candidate for treating neurodegenerative diseases such as Alzheimer's disease.

Several mechanisms of actions have been suggested for *Salvia species* extracts. Some hypothesis relates to their effects on the activity of pancreatic beta cells, increase of the insulin sensitivity or the insulin-like activity of the plant extracts and increase in the inhibitory effect against insulinase enzyme. Other mechanisms may also be involved such as increase of peripheral utilization of glucose, inhibition of intestinal glucose absorption, increase of synthesis of hepatic glycogen or decrease of glycogenolysis, decrease of glycemic index of carbohydrates and decrease of the effect of glutathione¹⁵ and improve response to insulin *in-vivo*²⁰.

CONCLUSION: In conclusion, this article presents a list of *Salvia species* that have hypoglycemic effects and can be used to treat various types of diabetes. Still, many antidiabetic herbs and their active compounds are not well defined, more research is needed to accurately

assess the mechanism of action of these plants. Studies have shown that sage and rosemary have phenolic compounds and their antioxidant properties are mainly due to the presence of carnosic acid and rosmarinic acid.

In addition, rosmarinic acid is one of the important phenolic compound of the genus *Salvia* and has many biological effects, such as antitumor, anti-hepatitis, inhibition of HIV-1 and hepatoprotection. In general, the extract of this plant, which has antioxidant and antiglycating effects, inhibits damage to the DNA, reduces lipid peroxidation, and protects nerve cells against H₂O₂.

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REFERENCES:

- Schaalan HSE-AaMF: Phytotherapy in diabetes: Review on potential mechanistic Perspectives. *World J Diabetes* 2014; (52): 176-97.
- A H: Antidiabetic drugs used in Europe prior to the discovery of insulin. *Pharmazie* 2007; 62: 717-720
- Khodaghali F and Saanasast F: Antioxidant and antiglycating activities of *Salvia sahendica* and its protective effect against oxidative stress in neuron-like PC12 cells. *J Nat Med* 2011; 65: 455-65.
- Afa Rguez K, Mejda D, Ikbel C, Bettaieb R and HammamiM: Chemical composition and biological activities of essential oils of *Salvia officinalis* aerial parts as affected by diurnal variations. *Plant Biosystems* 2018.
- Merigo FAB, Facchin S, Missaggia S, Bernardi P, Boschi F, D'Inca EVS R, Sbarbati A and Sturniolo G: Glucose transporter expression in the human colon. *World J Gastroenterol* 2018; 21(24): 775-93.
- Donohue DL: The Use of herbal supplements on minimizing the clinical manifestations of Alzheimer's disease. University of Central Florida 2017.
- Adejoh IP, Mark AU and Agatemor M: Anti-radical and Inhibitory Effect of some Common Nigerian Medicinal Plants on Alpha Glucosidase, Aldose Reductase and Angiotensin Converting Enzyme: Potential Protective Mechanisms against Diabetic Complications. *Int J Adv Res Biol Sci* 2018; (53): 188-201.
- Alkhalidy H, Wang Y and Liu D: Dietary Flavonoids in the Prevention of T2D. *An Overview Nutrients* 2018; (1043): 2-33.
- Yu RHH and Shlomo M: Insulin Secretion and Action. Humana Press 2005. 309-311.
- Lowe WL: Principles of Molecular Medicine. Humana Press 1998.
- Manukumar HM, Chandrasekhar B, Sri Raghava and Umsha S: Evidences for diabetes and insulin mimetic activity of medicinal plants. Present status and future prospects. *Critical Reviews in Food Science and Nutrition* 2017; 57(12): 2712-29
- Li Chen SZ, Mi Huang, XM, Jie Y, Shihao D, Yun H, Yanzhang W and Xinzhou Y: b-ecdysterone from *Cyanotis arachnoidea* exerts hypoglycemic effects through activating IRS-1/Akt/GLUT4 and IRS-1/Akt/GLUT2 signal pathways in KK-Ay mice. *Journal of Functional Foods* 2017; 39: 123-32.
- Eidi M and Zamanizadeh HR : Effect of *Salvia officinalis* L. leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats *Journal of Ethnopharmacology* 2005; 100: 310-3.
- Hui H TG and Go VLW: Hypoglycemic herbs and their action mechanisms. *Chin Med* 2009; 411.
- Bnouham M ZA, Mekhfi H, Tahri A and Legssyer A: Medicinal plants with potential antidiabetic activity-a review of ten years of herbal medicine research (1990-2000). *Int J Diabetes Metab* 2006; 14: 1-25.
- Borse RAA, Borse SL, Hamid, Patil S and Desai SG: Search for the Antidiabetic Plants. *Pharmacological Aspects. Pharmacologyonline* 2010; 1: 1023-30.
- Yuan LZRHA: Inhibition of phosphoenolpyruvate carboxykinase gene expression by metformin in cultured hepatocytes. *Chin Med J Engl* 2002; 115: 1843-8.
- Al BSe: Effect of *Salvia officinalis* on diabetic patients. *J Renal Inj Prev* 2013; 22: 51-4.
- Gayathri GAGM: Review on enhancement of glucose uptake and up-regulation of glucose transporters by antidiabetic medicinal plants. *Asian J Pharm Clin Res* 2016; 92: 34-39.
- Kareem T, Khashan KAA and Khefaji: Effects of *Salvia officinalis* L. (sag) leaves extracts in normal and alloxan - induced diabetes in white rats. *International Journal of Scientific & Engineering Research* 2015; 61: 20-8.
- Ashraf HHR, Nejati V and Ilkhanipoo M: Preventive effect of *Berberis integerrima* on the serum levels of glucose and lipids in streptozotocin induced diabetes in rats. *J Fasa Univ Med Sci* 2012; 2: 148-55.
- Mansouri EKL and Abedi HA: Antioxidant effects of proanthocyanidin from grape seed on hepatic tissue injury in diabetic rats. *Iran J Basic Med Sci* 2014; 17: 460-4.
- Sharma ASA, Chand T, Khardiya M and Yadav, KC: Antidiabetic and antihyperlipidemic activity of *Cucurbita maxima* duchense seeds on streptozotocin induced diabetic rats. *J Pharmacogn Phytochem* 2013; 1: 108-16.
- Nickavar B AL and Izadpanah H: α -Amylase inhibitory activities of six *Salvia* species. *Iranian J Pharm Res* 2008; 7: 297-303.
- Al Ze: Effects of ethanol extract of *Salvia hydrangea* on hepatic and renal functions of streptozotocin-induced diabetic rats. *AJP*. 2015; 52: 138-47.
- Amouoghli-Tabrizi B MD: Protective effect of turnip root ethanolic extract on early diabetic nephropathy in the rats. *Zahedan J Res Med Sci* 2011; 13: 13-9.
- Zarei A CAS, Taheri S and F R: Comparison between effects of different doses of *Melissa officinalis* and atorvastatin on the activity of liver enzymes in hypercholesterolemia rats. *AJP* 2014; 4: 1-9.
- Yakubu MT MI: Liver and Kidney Functional Indices of Pregnant Rats Following the Administration of the Crude Alkaloids from *Senna alata* Linn. Roxb Leaves. *Iranian Journal of Toxicology* 2012; 6: 615-25.
- Wu HY, MH-YGLSJHX and MXLJ: Constituents with-glucosidase and advanced glycation end-product formation inhibitory activities from *Salvia miltiorrhiza* Bge. *J Nat Med* 2011; 65: 37-42.

30. Rdoppwa-GAA: Recent development of plant products with anti-glycation activity: a review. RSC Adv 2015; 5: 31113-38.
31. María Porres-Martínez EGB, Emilia Carretero M and Pilar Gómez-Serranillos M: *Salvia* spp.: An Updated on Antioxidant Activity and Pharmacological Uses. Springer 2018; 151-77.
32. Azevedo CFL, Fernandes-Ferreira M, Almeida MJ, Pereira-Wilson and JMWaC: Rosmarinic acid, major phenolic constituent of Greek sage herbal tea, modulates rat intestinal SGLT1 levels with effects on blood glucose. Mol Nutr Food Res 2011; 55: 15-25.
33. Ramos AA, Azqueta A, Pereira-Wilson C, Collins AR: Polyphenolic compounds from *Salvia species* protect cellular DNA from oxidation and stimulate DNA repair in cultured human cells. J Agric Food Chem Toxicol 2010; 58: 7465-71.
34. Loizzo MR, Saab AM, Tundis R, Menichini, F Bonesi M, Piccolo GAS, Cindio BD, Houghton PJ and Menichini F: *In-vitro* inhibitory activities of plants used in Lebanon traditional medicine against angiotensin converting enzyme (ACE) and digestive enzymes related to diabetes. Journal of Ethnopharmacology 2008; 119: 109-16.
35. Kintzios ES: SAGE the Genus *Salvia*. Harwood Academic Publishers imprint 2005.
36. Harlev EEN, Mirsky N and Ofir R: Antidiabetic Attributes of Desert and Steppic Plants: A Review. Planta Med 2013; 79: 425-36.
37. Asadi SAA, Esmaeili MA, Sonboli A and Ansari NFK: *In-vitro* antioxidant activities and an investigation of neuroprotection by six *Salvia species* from Iran: a comparative study. Food Chem Toxicol 2010; 48: 1341-9.
38. Jequier C, Nicollier G, Tabacchi R and Garnero J: Constituents of the essential oil of *Salvia stenophylla*. Phytochemistry 1980; 19: 461-2.
39. Camarasa J, Canigueral S, Iglesias J and Marin E: Sur les aglycones flavoniques des feuilles de *Salvia verbenaca* L.: hydroxy-5 diméthoxy-7, 4' flavone, flavonoïde nouveau pour le genre *Salvia* L. Plantes médicinales et phytothérapie 1982; 16: 192-6.
40. Mancini ENAA, Martino LD, Feo VD and Formisano C: DRaFS: Chemical Composition and Phytotoxic Effects of Essential Oils of *Salvia hierosolymitana* Boiss. and *Salvia multicaulis* Vahl. var. *simplicifolia* Boiss. Growing Wild in Lebanon. Molecules 2009; 14: 4725-36.
41. Kharazian N: Flavonoid Constituents in Some Species of *Salvia* L. (Lamiaceae) in Iran Journal of Sciences, Islamic Republic of Iran 2014; 253: 219-27.
42. Meresa AWG, Basha H, Fekadu N, Tekla F, Ashebir R and Tadele A: Herbal Medicines for the Management of Diabetic Mellitus in Ethiopia and Eritria including their Phytochemical Constituents. American Journal of Advanced Drug Delivery 2017; 51: 40-58.
43. Salah MMA-CH, Shukri M and Rana IMLBK: Effect of *Salvia officinalis* L. (Sage) Aqueous extract on Liver and Testicular Function of Diabetic Albino Male Rats. Journal of Babylon University/Pure and Applied Sciences 2016; 242: 390-9.
44. Tepe B EO, Akpulat HA and Aydin E: Antioxidant potentials and rosmarinic acid levels of the methanolic extracts of *Salvia verticillata*. Food Chem Biol Interact 2007; 1003: 985-9.

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