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Research Article

Hypoglycaemic and Hypolipidemic Effects of Alcoholic Extract of Common Sage (*Salvia Officinalis*) In Streptozotocin –Induced Diabetic Rabbits

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ABSTRACT

The hypoglycaemic and hypolipidemic effect of alcoholic extract of common sage (*Salvia officinalis*) on streptozotocin-induced diabetic rabbits was evaluated. Twenty-five male rabbits were used and grouped as follows: - Group A- Diabetic control, Group B - Diabetic rabbits + glibenclamide (0.25 mg/kg), Group C - Diabetic rabbits + alcoholic leaf extract at 250 mg/kg and Group D - Diabetic rabbits + leaf extract at 500 mg/kg. Group E- served as normal non-diabetic control. The animals were given a standard diet and water *ad libitum.* Diabetes was induced in the rabbits by a single intra-peritoneal injection of freshly prepared streptozotocin 50 mg/kg b.w. followed by 120 mg/kg of nicotinamide in 0.1 M citrate buffer, pH 4.5 in a volume of 0.5 ml/kg b.w. Blood samples were collected on the 1st, 7th, 14th and 21st days from the marginal ear vein of the animals and analysed for blood glucose and lipid profile levels. The standard/investigational drugs treated rabbits showed a marked decrease in the level of blood glucose when compared with the diabetic control at a significant level of $p < 0.001$. The alcoholic extract of common sage leaf (at 250mg/dl and 500mg/dl) showed a significant decrease ($p < 0.05$) in blood glucose compared with the diabetic control rabbits. The administration of the leaf extract at 250mg/dl and 500mg/dl to the animals prevented gross alterations in the lipid profile levels.

Keywords: Hypoglycaemia, Hypolipidemia, *Salvia officinalis*, Diabetes mellitus

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INTRODUCTION

*Salvia officinalis*is also commonly called common sage, sage, garden sage, kitchen sage, golden sage, true sage, dalmatian sage, culinary sage and broadleaf sage. *Salvia officinalis*(Figure 1) is a much-branched evergreen shrub growing 50 - 100cm tall. It is an aromatic and a perennial plant used as flavoring spices and as herbal medicine (Ayatollahi *et al*., 2009). It has also been used for the treatment of ailments such as cough, asthma, angina, digestive and circulation disturbances, bronchitis, throat inflammations, depression, and skin diseases (Midling *et al.*, 2008; Rami and Li, 2011). Its essential oils have also been used in the treatment of some ailments such as neurological, heart, metabolic and endocrine diseases. The essential oils also have antispasmodic and astringent properties (Khan *et al.*, 2011; Loizzo *et al*., 2007).

Some of the main substances in *S. officinalis* are: 1,8-cineole, camphor, bornyl acetate, borneol, camphene, α- and β-thujone, α- and β-caryophyllene, α-humulene, α- and β-pinene, linalool, viridiflorol, pimaradiene, rosmarinic acid, salvianolic acid, carnosolic acid and ursolic acid, etc. (Rami and Li, 2011; Radulescu *et al*., 2004). The main components in its essential oil are 1,8-cineole, α-thujone, β-thujone, camphor, borneol, and viridiflorol **(**Croteau *et al.*, 1981).

Salvia species have been shown to be beneficial in the treatment of cerebral ischemia, memory disorders, depression, lost or declining memory and Alzheimer's disease (Mohsen *et al*., 2014; Imanshadi and Hosseinzadeh, 2006; Eidi *et al.*, 2006). Medical plants have been used extensively and successfully in the treatment of many health conditions (Avwioro *et al* 2010a; Avwioro,2012; Onyije and Avwioro 2012) and sage is one of them. Diabetes mellitus (DM) is a group of metabolic disorders of carbohydrate metabolism

characterized by hyperglycaemia. It occurs as a result of defects in insulin secretion, insulin action or both (Rang *et al*., 2014).

Diabetes mellitus is a threat to public health and a major challenge of the 21st century (Zimmet *et al.*, 2014**)**. It can also be described as a generalised metabolic disease characterized by abnormality in carbohydrate, lipid and protein metabolism. The basic defect is a relative or absolute lack of insulin, which can be managed. However, there are some challenges in the management of DM (Xiang *et al.*, 2007). Diabetes mellitus was responsible for 1.6 million deaths worldwide in 2016 with increase in morbidity and mortality over the years (WHO/IDF. 1999). Diabetes mellitus is a multifactorial disease characterized by hyperglycaemia and lipoprotein abnormalities which is characterized by elevated levels of cholesterol, triglycerides and changes in lipoproteins (Majekodunmi *et al*., 2011). The prevalence of diabetes is high in Nigeria and even more worrisome is the proportion of hyperglycaemia in those without a previous diagnosis which is as high as 6% in a studied population (Rajaei *et al.*, 2015). Pharmaceutical studies on plants revealed that about 75-85% of the world population, particularly in the developing countries employ plant based medications for the management of host of ailments in humans (Oghenekaro *et al.*, 2020). Studies abound that bioactive compounds like cumarins, flavonoids, terpenoids and other secondary metabolites have been found in medicinal plants often used for the management of diabetes (AIT, 2010). Therefore, the need for the search of a more reliable and perhaps safe and effective management methods for DM using medicinal pharmacological plant alternative such as common sage (*Salvia officinalis*) necessitates this study on common sage leaf extracts.

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MATERIALS AND METHODS

All chemicals and reagents used were of analytical grade.

Plant Material: Fresh samples of *Salvia officinalis*plant was obtained in Vom-Jos, Plateau state, Nigeria. The plant was identified and authenticated by a Botanist from the University of Jos Herbarium, deposited and voucher saved. The leaves were removed from the stalk, rinsed with distilled water and air dried at room temperature (28±2ºC), after which it was ground with a sterilized blender and sieved to coarse powder. The powdered *Salvia officinalis*leaf (50g) was weighed and soaked in 400ml of absolute methanol, for 3 days. The mixture was filtered using mushing cloth. The filtrate was concentrated using soxhlet machine. The extract obtained was kept in airtight sample bottles and stored in the refrigerator.

Experimental Animals: Apparently healthy male rabbits of weight 950g- 1150g were used for the study. They were obtained from the Rabbit Section of the Dagwom Farm, National Veterinary Research Institute (N.V.R.I), Vom-Jos, Plateau State-Nigeria. The animals were screened for infection before use, housed in standard cages and kept under standard condition. The study had approval of Delta State Faculty of Science constituted Ethical Committee. It was also carried out according to the principles for care and use of laboratory animals. The animals were given a standard diet and water *ad libitum* and allowed to acclimatize to the laboratory environment for 2 weeks before proceeding with the study.

Acute Oral Toxicity Study (Determination of LD_{50}): The OECD GUIDE (2002) was utilized with the help of Hodge and Sterner scale for the determination of the LD_{50}. Each rabbit had oral doses of the common Sage leaf extract as follows: 0, 10, 100, 300, 2000, 5000 and 6000mg/kg.

Induction of diabetic animals: After an overnight-fast, diabetes was induced in the rabbits by a single intra-peritoneal injection of freshly prepared streptozotocin 50 mg/kg b.w. followed by 120 mg/kg of nicotinamide in 0.1 M citrate buffer, pH 4.5 in a volume of 0.5 ml/kg b.w. Diabetes was confirmed in the rabbits after 48 hours post induction and animals with fasting blood glucose of more than 200 mg/dl were taken as diabetics.

Plate 1
Sage officinalis leaves.

Experimental design: The diabetic animals were randomly assigned into four Groups (A, B, C, D) and with Group E as Normal non-diabetic control of five rabbits each. Group A- Diabetic control, Group B - Diabetic rabbits treated with glibenclamide (0.25 mg/kg), Group C - Diabetic rabbits treated with the extract of 250 mg/kg and Group D - Diabetic rabbits treated with the extract of the common Sage(*Salvia officinalis*) leaf 500 mg/kg. The dosses were based on previous documented reports (Petchi *et al.*, 2013). Fasting blood glucose level was assayed 24 and 48 hours post diabetes induction treatment using a commercial auto coding Glucometer (Accu check). The animals were given the extracts doses once every morning by oral compulsory oral intubations before meals. While the glibenclamide drug was also given once daily through oral route for 21 consecutive days.

Sample Collection: About 1 ml of blood sample was collected on the 1st, 7th, 14th and 21st day from the marginal ear vein of the animals, into heparinized tube, properly mixed and labelled with dates. The collected plasma was used immediately for the analysis. Body weight of the rabbits were taken on the 1st to the 21st days. At the end of the experiment, the animals were sacrificed and the heart, kidneys, liver, pancreas and spleen removed washed with physiological saline. Then their weights were taken and noted.

Determination of Blood Glucose and other Biochemical parameters: Randox assay kits (Crumlin, UK) (Friedewald *et al.*, 1972) were used for the estimation of the animals' plasma glucose, total cholesterol, triglycerides and HDL-cholesterol using an Auto-Analyzer (Midray: BA-88A). LDL levels were calculated according to standard method (Onyije *et al.*, 2012).

Statistical Analysis: The data were expressed as mean ± SEM. Level of significance between groups was done using one-way ANOVA and followed by Dennett's post-hoc test. A *p-value* of less than 0.05 ($p < 0.05$) was considered significant.

RESULTS

The extract of *Salvia officinalis*at both doses (250mg/dl and 500mg/dl) significantly increased ($p < 0.05$ or $p < 0.001$) the body weight of the rabbits when compared with the diabetic control. Also the standard drug glibenclamide treated diabetic rabbit significantly increased ($p < 0.001$) the body weight of the rabbit when compared with the diabetic control (In Table 1).

In Table 2, the extract at both doses showed an equally significant decrease ($p< 0.050$) in the weight of the heart, kidneys, liver and the pancreas. While, there is a significant increase ($p < 0.05$) in the weight of the spleen when compared with the diabetic control rabbits.

Table 3 shows the effect of alcoholic extract of common Sage (*Salvia officinalis*) leaf on blood glucose levels in streptozotocin-induced diabetic rabbits. In this study, the diabetic control rabbits showed a marked increase in the blood glucose levels from the first day of 260.40 ± 3.36mg/dl to 354.00 ± 1.36mg/dl on the 21 first day. Also, the standard investigational drugs treated rabbits showed a marked decrease in the level of blood glucose when compared with the diabetic control at a significant level of $p < 0.001$. Equally, the alcoholic extract of common sage leaf (at 250mg/dl and 500mg/dl) showed marked decrease in the blood glucose levels, from the first week of the streptozotocin-induced diabetic rabbits to the third week of administration. The alcoholic extract of common sage leaf (at 250mg/dl) showed a significant decrease ($p < 0.05$) compared to diabetic control rabbits. Likewise, the alcoholic extract of common sage leaf (at 500mg/dl) showed a significant decrease ($p < 0.001$) in the blood glucose levels when compared with the diabetic control group.

Table 1:
Effect of methanol extract of common Sage (*Salvia officinalis*) leaf on body weight of streptozotocin-induced diabetic rabbits

Animal Groups	Body weight (g)			
	1ST Day	7TH Day	14TH Day	21ST Day
A (Diabetic Control)	1028 ± 1.16	1020 ± 1.10	1018 ± 0.97	1018 ± 2.10
B (Diabetic + glibenclamide)	1030 ± 1.10	1035 ± 1.12*	1040 ± 1.46*	1042 ± 1.34*
C (Diabetic + 250mg/dl Sage l)	1126 ± 1.17	1136 ± 0.90**	1138 ± 1.12**	1148 ± 2.16**
D (Diabetic + 500mg/dl Sage l)	1096 ± 3.16	1150 ± 2.16**	1160 ± 1.87**	1162 ± 2.26**
E (Normal Control)	1098 ± 1.12	1110 ± 1.51	1112 ± 0.96	1113 ± 1.50

Value expressed as mean ± SEM (n=5) *p < 0.05, **p < 0.001 compared with diabetic control

Table 2:
Effect of methanol extract of common Sage (*Salvia officinalis*) leaf on rabbits' organs of streptozotocin-induced diabetic rabbits

Animal Groups	Organs (g)				
	Heart	Kidney	Liver	Pancreas	Spleen
A (Diabetic Control)	1.80 ±0.14	2.50 ±1.12	8.16 ±0.06	1.25±0.15	0.75±0.02
B (Diabetic + glibenelamide)	0.780±0.08*	0.96±0.04*	4.46±0.36*	0.45 ±0.18*	1.65±0.01*
C (Diabetic + 250mg/dl Sage l)	0.81±0.04*	0.95±0.46*	4.26±0.81*	0.45 ±0.04*	1.75±0.06 *
D (Diabetic + 500mg/dl Sage l)	0.75±0.31*	0.93±0.36*	4.08±0.16*	0.46 ±0.06*	1.60 ±0.36*
E (Normal Control)	0.76 ±0.60	0.96±0.03	3.10 ±0.27	0.40 ±1.12	1.56 ±0.04

Value expressed as mean ± SEM (n=5) * p < 0.05 compared with diabetic control

Table 3:
Effect of methanol extract of common Sage (*Salvia officinalis*) leaf on blood glucose levels in streptozotocin-induced diabetic rabbits

Animal Groups	Blood glucose (mg/dl)			
	1ST Day	7TH Day	14TH Day	21ST Day
A (Diabetic Control)	260.40 ± 3.36	298.00 ± 2.12	320.1 ± 0.62	354.0 ± 1.36
B (Diabetic + glibenelamide)	258.10 ± 2.81	192.00 ± 4.10**	154.0 ± 3.10**	115.0 ± 2.34***
C (Diabetic + 250mg/dl Sage l)	256.40 ± 2.89	230.10 ± 4.12**	190.1 ± 2.16**	161.0 ± 1.86***
D (Diabetic + 500mg/dl Sage l)	253.70 ± 4.27	198.62 ± 2.16***	178.28 ± 1.62***	119.30 ± 2.12***
E (Normal Control)	81.20 ± 1.26	80.40 ± 1.12	78.80 ± 1.38	80.90 ± 1.21

Value expressed as mean ± SEM (n=5) **p < 0.05, *** p < 0.001 compared with diabetic control

Table 4:
Effect of methanol extract of common Sage (*Salvia officinalis*) leaf on lipid profile in streptozotocin-induced diabetic rabbits (mg/dl)

Animal Groups	Total cholesterol	Triglycerides	HDL cholesterol	LDL cholesterol
A (Diabetic Control)	85.16 ± 1.36	106.13 ± 0.76	26.47 ± 0.18	61.82 ± 0.16
B (Diabetic + glibenelamide)	64.81 ± 0.18*	83.10 ± 1.02*	24.18 ± 0.18	31.69 ± 0.82*
C (Diabetic + 250mg/dl Sage l)	51.01 ± 0.65*	72.26 ± 0.75*	30.01 ± 0.05	33.14 ± 2.00*
D (Diabetic + 500mg/dl Sage l**)**	56.61 ± 0.82*	70.86 ± 0.76*	28.81 ± 0,02	29.98 ± 0.12*
E (Normal Control)	50.20 ± 1.01	65.50 ± 0.10	35.10 ± 0.28	34.90 ± 0.16

Value expressed as mean ± SEM (n=5) *p < 0.05 compared with diabetic control

Table 4 shows the effect of alcohol extract of common sage (*Salvia officinalis*) leaf on lipid profile in streptozotocin-induced diabetic rabbits. The table revealed significant increase ($p < 0.05$) in the total cholesterol, triglycerides, LDL cholesterol and reduction in the level of HDL cholesterol in the diabetic control rabbits compared with the normal control rabbits. Also, the administration of the alcoholic extract of common sage (at 250mg/dl and 500mg/dl) to the streptozotocin-induced diabetic rabbits prevented the gross alterations in the lipid profile levels

DISCUSSION

Medicinal plants have been very useful in traditional medicine (Onyije *et al.*, 2012; Abubakar *et al.*, 2022) and have been of particular importance in low income countries. The administration of alcoholic extract of common sage leaf at both 250mg/dl and 500mg/dl kg body weight revealed significant hypoglycaemic effect on streptozotocin-induced diabetic rabbits. The hypoglycaemic activity of the common sage plant leaf is comparable to that of the standard drug glibenclamide commonly used for the management of such disease. A previous study had noted that common sage plant leaf contains high concentrations of flavonoids and saponins amongst other phytochemicals (Ayatollahi *et al.*, 2009). The suggestion, along with another studies that the hypoglycaemic activity may be due to the individual or synergistic action of flavonoids and saponins in the plant is well noted (Tiwari and Rao 2002; Mokogwu *et al.*, 2022). *S. miltiorrhiza* or Chinese sage has similar metabolite profile to common sage. The extract has been found to lower plasma cholesterol, triglycerides and low density lipoprotein. It increases high density lipoprotein level (Christensen *et al.*, 2010). Studies have shown that the extract of *S. officinalis* activates peroxisome proliferator-activated receptor gamma, a regulator of genes for energy, lipid and glucose metabolism. This helps to improve the ratio of high density lipoprotein to low density lipoprotein. It lowers triglycerides in serum and reduces insulin resistance (Christensen *et al.*, 2010). Previous studies have shown that the extracts are effective in the prevention of LDL-cholesterol oxidation, thereby reducing cardiovascular disease (Sa *et al.*, 2009). The extract *S. officinalis* possesses insulin-like substances and it is for this reason, that it *i*s a traditional remedy for diabetes in many regions (Christensen *et al.*, 2010) but the traditional healers have not established safe dosage for the treatment of diabetes. Its methanolic extract has been found to significantly decrease serum glucose level in Type I diabetic rats without significantly affecting pancreatic insulin production (Christensen *et al.*, 2010). Studies have shown that people who drink about 300ml sage tea twice a day have an increased antioxidant defenses as well as improved lipid profile, without any adverse effects (Sa *et al.*, 2009). However, prolonged use and the overdose of the ethanolic extract of the oil of *S. officinalis* in excess of 15 g of the leaves can have side effects which may include vomiting, tachycardia, tongue swallowing, and convulsion (Bown, 1995; Mills and Bone, 2005).

In conclusion, the alcoholic leaf extract of *Salvia officinalis*exhibits antidiabetic activity on streptozotocin-induced diabetes mellitus in rabbits. The leaves of the plant may be used in the local management of diabetes mellitus.

Authors Contributions
MATH and AOG conceived this work. MATH, ACO, OUH, IJO and EOB carried out the experiments. MATH and AOG performed the statistical analysis. MATH drafted the manuscript. All authors read and approved the final manuscript.

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