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Research Article

Antidiabetic and Hypoglycaemic Activities of Commonly Used African Traditional Vegetables

Nolitha Nkobole[1,*], Lavhelesani R. Managa[2], Gerhard Prinsloo[1]

ABSTRACT

Introduction: Diabetes mellitus is a common and complex metabolic disorder associated with high blood glucose levels leading to complications. Adopting a sedentary lifestyle characterized by low physical activity and consumption of high-energy diets contributes to the development of diabetes mellitus. Lifestyle changes and the use of pharmacological agents that target particular biochemical pathways involved in nutrient metabolism are currently used as management guidelines for managing risk factors associated with diabetes mellitus. The use of prescription medications for an extended period is linked to several negative side effects. Alternative management strategies of risk factors linked to diabetes mellitus involve the use of African leafy vegetables. African leafy vegetables contain a variety of biologically active compounds that provide health benefits. These crops have the potential to be a valuable source of new oral hypoglycemic agents for diabetes management. This review analyses the antidiabetic activities of nine African leafy vegetables whilst also defining the gap areas for future research. **Methods**: Data was acquired via electronic search engines of which only peer-reviewed papers published in journals were considered. **Results**: African traditional vegetables showed diverse *in vitro* and *in vivo* antidiabetic activities. **Conclusions**: There is an urgent need to document and use the knowledge of African leafy vegetables that have potential in the treatment and management of diabetes mellitus.

Key words: Antidiabetic, Hypoglycaemic, African traditional vegetables, Diabetes mellitus, Phytochemicals.

Nolitha Nkobole[1,*], Lavhelesani R. Managa[2], Gerhard Prinsloo[1]

[1]*Department of Agriculture and Animal Health, University of South Africa, Science campus, Florida, SOUTH AFRICA.*

[2]*Africa Institute of South Africa, Human Sciences Research Council, Pretoria, SOUTH AFRICA.*

Correspondence

Nolitha Nkobole

Department of Agriculture and Animal Health, University of South Africa, Science campus, Florida, SOUTH AFRICA.

E-mail: nkobon@unisa.ac.za

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterised by abnormal glucose, protein and lipid metabolism, resulting in an elevated plasma glucose level.[1] Diabetes is also associated with polyurea, weight loss, muscle weakness, polydipsia, polyphagia, and hyperlipidaemia and hyperglycaemia. Insulin suppresses the function of lipase-stimulating hormones in adipose tissue.[2] When insulin is not functioning optimally, the rate of lipolysis rises releasing free fatty acids into the bloodstream; this also increases β-oxidation of fatty acids and cholesterol. Insulin also mediates cholesterol elimination; thus, its absence results in hyperlipidaemia and hypercholesterolemia in diabetes.[2]

According to the World Health Organisation (WHO) data, 400 million people worldwide have diabetes, with approximately 1.5 million deaths, and this rate is expected to double by 2035 due to people's affluent lifestyles.[3,4] If blood sugar levels are not controlled, it can have a major influence on multiple organs, leading to ailments such as hypertension, kidney disease and blindness. Diabetes treatment is costly, and it also has negative side effects such as weight gain and gastro-intestinal issues. Furthermore, people find it difficult to adjust to lifestyle changes such as consuming sugar-free foods. As a result, it is critical to seek out alternate methods of controlling blood sugar.[5]

Food plants with promising therapeutic potential and few adverse effects are gaining attention and acknowledgment for diabetes control. Unlike pharmaceutical antidiabetic medicines, which are laden with notable side effects, wild plants do not have these side effects and do not require a strict regimen because they can be consumed as food.[5] The various mechanisms by which plant drugs demonstrated anti-diabetic activity include glycosidase (glucosidase) inhibition, α-amylase inhibition, and inhibition of hepatic glucose metabolizing enzyme.[6] Furthermore, plant foods can be effective by stimulating insulin production or acting as an insulin mimic, stimulating glycogenesis, reducing the release of glucagon and other hormones that counteract insulin action, antioxidant mechanism, preventing glycosylation of haemoglobin and regulating glucose absorption from the gut.[5] This review article enumerates some commonly consumed wild plants in South Africa possessing antidiabetic activity. The nine vegetables are Chinese cabbage (*Brassica rapa*), pigweed (*Amaranthus* species), Jew's mallow (*Corchorus olitorius*), spider flower (*Cleome gynandra*), pumpkin (*Cucurbita pepo*), purslane (*Portulaca oleracea*), tsamma melon (*Citrullus lanatus*), blackjack (*Bidens pilosa*) and white goosefoot (*Chenopodium album*). The vegetables were chosen on the basis of popularity.[7,8]

MATERIALS AND METHODS

Literature search was conducted using Google Scholar, Pubmed, Scopus, Science Direct, ProQuest and Web of Science. Search terms included 'African/traditional/indigenous leafy vegetables', separately and in combination with their common names, namely 'pigweed', 'pumpkin', 'spider flower', 'purslane', 'blackjack', 'Jew's mallow', 'Chinese cabbage' and 'tsamma melon'. Scientific names including 'Amaranthus species', 'Cucurbita pepo', '*Cleome gynandra*', '*Portulaca oleracea*', '*Bidens*

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pilosa', '*Corchorus olitorius*', '*Brassica rapa*', '*Citrullus lanatus*' and '*Chenopodium olitorius'* were used separately and in combination with 'diabetes mellitus', 'antidiabetic', 'hypoglycaemic', 'antihyperglycemic' and 'type-2 diabetes'. The search was limited to only peer reviewed papers published in English, and therefore theses and dissertations were excluded. In addition, references of the articles were also searched. To be included in this study, the plant materials should be eaten as part of the diet. All articles that addressed indigenous medicinal plants and trees as well as indigenous fruits not consumed as vegetables, were also excluded. A total of 2 021 articles were retrieved of which only 192 matched the inclusion criteria for the review.

RESULTS AND DISCUSSION

Extraction of wild foods

The *in vivo* antidiabetic activities of the crude extracts and solvent fractions of different wild vegetable parts using different chemicals were investigated as displayed in figure 1. Among solvents, aqueous was the most commonly used solvent for the extraction of plants, followed by ethanol and methanol solvents. Some studies tested for antidiabetic effects using dried plant parts, juice prepared from the leaves, and other methods.

In vitro studies

In vitro studies that were undertaken to assess commonly consumed wild foods in South Africa involve the use of cell culture and the use of carbohydrate-hydrolysing enzymes, α-amylase and α-glucosidase. Glucose uptake in the skeletal muscles and adipose tissue is critical for the reduction of postprandial blood glucose concentrations in people with type-2 diabetes mellitus.[9]

A total of 34 *in vitro* studies were reported with α-amylase and α-glucosidase (n = 15) being the most commonly used enzymes, followed by studies that investigated only one of the enzymes with α-amylase (n = 10) being the most common, and closely followed by α-glucosidase (n = 4). Significant differences in concentrations were reported from 1.70 and 1.60 µg/ml up to as high as 0.19 mg/mL and 0.32 mg/mL for α-amylase and α-glucosidase respectively. Similar to the *in vivo* studies, most studies (n = 7) were performed on *P. oleraceae* followed by *C. lanatus* (n = 5), *C. olitorius* and *C. pepo* (both n = 4), although the group of *Amaranthus* spp. in combination showed the most reports (n = 8).

(E)-5-hydroxy-7-methoxy-3-(2'-hydroxybenzyl)-4-chromanone (HM-chromanone) isolated from *P. oleracea* showed a significant increase in glucose uptake in 3T3-L1 adipocytes by stimulating translocation of GLUT4 to the plasma membrane.[10] HM-chromanone also promoted glucose uptake into L6 skeletal muscle cells in a dose-dependent manner. Notably, *Portulaca oleracea* exhibited more α-glucosidase and α-amylase activities when compared with the reference drug (acarbose).[11] In addition, *Chenopodium album* inhibited α-amylase enzyme more effectively than conventional acarbose.[12] The *in vitro* antidiabetic activities of commonly consumed wild foods, which have been investigated in South Africa, are summarized in table 1.

In vivo studies

A total of 96 studies were reported, which is a very high number of *in vivo* studies that have already been conducted with most using mice and rats as experimental animals. Of the 96 studies that were conducted, the STZ-induced rat model was the most common (n = 50) followed by the Alloxan-induced rat model (n = 37). Most studies found positive results at activity of 50 to 800 mg/kg bw, although concentrations as low as 1.25 mg/kg bw and as high as 2 000 mg/kg bw have been reported with positive results. It is however interesting that in the majority of studies the control (mostly glibenclamide and metformin) showed activity at much lower concentrations than the extracts. It would therefore seem as if the extract is not as effective as the known anti-diabetic drugs as the majority of the plants were more effective at higher concentrations than the positive controls. The most studies (n = 29) were performed on *P. oleraceae* followed by *C. lanatus* (n = 19) and *C. olitorius* (n = 12) with positive results reported for all of them. There was significant variance in the duration of treatment among *in vivo* studies, ranging from 2 hours to 18 weeks. Noteworthy, significant acute blood glucose level control was reported in all the plants (Table 2).

CONCLUSION

An extensive literature survey was performed on commonly consumed wild foods in South Africa, namely *Portulaca oleracea*, *Citrullus lanatus*, *Bidens pilosa*, *Amaranthus* spp., *Brassica rapa*, *Chenopodium album*, *Cucurbita pepo* and *Cleome gynandra*. Alloxan- and streptozotocin-induced diabetic rats and mice were commonly used as the model to assess the antidiabetic activity for preclinical *in vivo* studies (Table 2). *In vitro* antidiabetic activity was mostly conducted using α-amylase and α-glucosidase inhibition assays. Some of the mechanisms of action for reported plants include improvement in insulin sensitivity and pancreatic β-cell function (Table 1).

Antidiabetic active compounds such as 1-4, (E)-5-hydroxy-7-methoxy-3-(2'-hydroxybenzyl)-4-chromanone, cytopiloyne, stearic acid ethyl ester, 3-beta-D-glucopyranosyloxy-1-hydroxy-6(E)-tetradecene-8,10,1 2-triyne, 2-beta-D-glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne, 3-beta-D-glucopyranosyloxy-1-hydroxy-6(E)-tetradecene-8,10,12-triyn, methyl 4-O-caffeoyl-2-C-methyl-D-erythronate, 4-O-methylokanin, – (14E, 18E, 22E, 26E) – methyl nonacosa-14, 18, 22, 26 tetraenoate, indole-3-acetonitrile, 4-methoxyindole-3-acetonitrile, indole-3-aldehyde, flavonoids, liquiritin, licochalcone A, sinapic acid, caffeic acid, 2-phenylethyl β-glucopyranoside, salidroside, syringic acid, adenosine, (3β, 20E)-ergosta-5, 20 (22)-dien-3-ol, Licochalcone A, caffeic acid, palmitic acid, pheophorbide A-methyl ester and α-spinasterol were isolated from some of the wild plants. Given the large number of *in vivo* studies, it could be expected that more compounds would have been isolated and tested.

Even though all the plants have been extensively studied for their antidiabetic activity, better results were rarely reported than the drugs acarbose and glibenclamide used as positive controls. Noteworthy is that much more *in vivo* studies (n=96) have been reported than *in vitro* studies (n=34), which is unexpected as *in vitro* studies are normally used as an indicator potential to be tested further for *in vivo* activity.

Surprisingly, only three plants, *P. oleracea*, *B. pilosa* and *A. cruentus*, have been subjected to clinical trials, given the large number of *in vivo* studies conducted. The majority of the methodology used for clinical trials was not appropriately designed and hence led to inconclusive findings. This therefore creates an opportunity and need for exploring wild foods in clinical trials. In addition to antidiabetic activities, the reported wild foods extracts showed an improvement of lipid profile parameters. As a result, it was demonstrated that these plant extracts might be used to treat diabetes mellitus complications and risk factors. However, more research is warranted to investigate and underline in-depth mechanisms of action towards the management of diabetes mellites, associated complications and to isolate antidiabetic active constituents. All the plants reported in this study describe the potential of these plants to aid in the treatment of diabetes as part of the diet by consumption of indigenous vegetables. The review present strong support for well-designed clinical trials and the development of novel antidiabetic drugs from the indigenous leafy vegetables discussed in this review. This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.

Table 1: Summary of *in vitro* antidiabetic activity of African widely consumed wild foods.

Scientific name	Common name	Extract/ Compound	Model	Dose		Results	Reference
		E)-5-hydroxy-7-methoxy-3-(2'-hydroxybenzyl)-4-chromanone	INS-1 Pancreatic β Cells	1, 5, 10, 20 µM		Protection of the pancreatic β-cell from high glucose-induced oxidative stress and apoptosis.	[10]
		Ethanol extract	INS-1 Pancreatic β Cells	0.1, 0.2, 0.5, 1.0, or 2.0 mg/mL		Significantly increased insulin secretion dose-dependently.	[13]
		(E)-5-hydroxy-7-methoxy-3-(2'-hydroxybenzyl)-4-chromanone (HM-chromanone).	L6 skeletal muscle cells	Compound=1,3,5,8,10,15,20 and 30µM. Positive control=100nM (insulin).		Promoted glucose uptake into L6 skeletal muscle cells dose dependently.	[14]
Portulaca oleracea	Purslane	*Fresh and dried extract	HepG2 cells	Cells were treated with 10-9 mol/L insulin and fresh/ dry plant material (0.25, 05 and 1.0 mg/ mL). Metformin=0.086 mg/mL.		Significantly increased extracellular glucose consumption by insulin resistant HepG2 cells (P <0.05).	[15]
		Methanol water	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 45.05 mg/mL, acarbose=IC_{50}=35.5 mg/mL	α-amylase IC_{50} 488.49 mg/mL, acarbose= 50 mg/mL		[16]
		Methanol/water (8:2)	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 0.168 mg/mL, acarbose= 0.295 mg/mL	α-amylase IC_{50} 0.212 mg/mL, acarbose= 0.334 mg/mL	Significantly reduced α-glucosidase enzyme than acarbose. Significantly inhibited α-amylase enzyme.	[11]
		(E)-5- hydroxy-7-methoxy-3-(2'-hydroxybenzyl)-4-chromanone	3T3-L1 adipocytes.	20µM		Significant increased glucose uptake in 3T3-L1 adipocytes by stimulating translocation of GLUT4 to the plasma membrane.	[9]
		Methanol	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 627.270 µg/mL, acarbose= 482.188 µg/mL	α-amylase IC_{50} 58.558 µg/ mL, acarbose= 47.880 µg/mL		[17]
		Methanol/water: 7:3	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 32.50 µg/mL, acarbose=18.57 µg/mL	α-amylase IC_{50} 58.51 µg/mL, acarbose=48 µg/ mL	Exhibited a remarkable α-glucosidase and α-amylase inhibitory activity.	[18]
Citrullus lanatus	Tsamma melon			α-glucosidase IC_{50} 54.44 µg/mL	α-amylase IC_{50} 76.68 µg/mL	Demonstrated the best inhibitory activity against α- glucosidase and a mild inhibitory activity against α-amylase.	[19]
		i) Alcalase and ii) tryptic hydrolysates from *C. lanatus*	α-Amylase	i) 0.149 ii) 0.234 mg/mL		Exhibited potent α-amylase inhibitory ability in a dose-dependent manner.	[20]
		Hexane	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 34.41 µg/mL, acarbose=35.5 µg/mL	α-amylase IC_{50} 421 µg/mL, acarbose=35.5 µg/mL	Showed significant α-glucosidase inhibition and weak α- amylase inhibition.	[21]
		Methanol	α-Amylase	72.15 µg/mL, acarbose=80.5 µg/mL		Showed higher potency than acarbose.	[22]
		Aqueous	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 1.60 µg/mL	α-amylase IC_{50} 1.70 µg/mL	Significantly ($p < 0.05$) inhibited α-amylase and α-glucosidase activities dose-dependently	[23]
Corchorus olitorius	Jew's mellow	Corchoruside A	α-Glucosidase	0.18Mm, acarbose =0.62Mm.		The compound was three-fold more potent than acarbose in inhibiting α-glucosidase inhibition.	[24]
		i) Free polyphenol extract, ii) bound polyphenol extract	α-Amylase and α-glucosidase	α-glucosidase IC_{50} i) 21.5 µg/mL, ii) 29.4 µg/mL	α-amylase IC_{50} i) 26.8 µg/mL, ii) 54.8 µg/mL	Extracts inhibited α-amylase and α-glucosidase in dose-dependent manner	[25]
		Methanol	α-Amylase and α-glucosidase	α-glucosidase IC_{50} 41.64 µg/mL^{-1}, acarbose=21.38 µg/mL^{-1}	α-amylase IC_{50} 27.95 µg/mL^{-1} acarbose=21.38 µg/mL^{-1}		[26]

			α-Amylase		α-amylase 92.75 ± 0.34% inhibition at 5 mg/mL. acarbose inhibited α-amylase by 99.21 ± 0.32 at 1 mg/mL.	The leaves of *B. pilosa* showed a 92.75 ± 0.34 inhibition on α-amylase activity at 5 mg/mL. Acarbose which was tested at 1 mg/mL caused a 99.21 ± 0.32 inhibition activity	[27]
Bidens pilosa	Black jack	n-hexane	α-Glucosidase	α-glucosidase IC_{50} 235.8 μg/mL		Demonstrated in vitro α-glucosidase inhibitory activity	[28]
		chloroform		α-glucosidase IC_{50} 125.6 μg/mL			
		aqueous		α-glucosidase IC_{50} 100.3 μg/mL			
		caffeoylquinic acid derivatives		α-glucosidase IC_{50} 214.5 μM		Showed significant α-glucosidase inhibitory activity	
Amaranthus species							
		Methanol			α-amylase 19.233 μg/mL	Inhibited α-amylase activity significantly	[29]
		Acarbose			0.312 μg/mL		
A. caudatus		Oscar blanco seeds methanol extract	α-amylase	94.7 ±0.008 %		Inhibited α-amylase activity	[30]
		Victor red seeds methanol extract		95.1±0.001%			
		Acetone	α-amylase and α-glucosidase	α-glucosidase 78%	α-amylase 46%	Showed moderate α-amylase enzyme inhibition and strong α-glucosidase inhibition	[31]
			α-amylase and α-glucosidase	α-glucosidase 40%	α-amylase 35%	Showed moderate α-amylase and glucosidase enzyme inhibition	[32]
A. cruentus	Pigweed	Methanol	α-amylase	IC_{50} value of 46.73 mg/mL			[33]
		Unprocessed leaf		α-glucosidase IC_5 0.32 mg/mL	α-amylase IC_{50} 0.19 mg/mL	inhibited α-amylase and α-glucosidase activities in a dose dependent manner.	[34]
		Methanol	α-amylase and α-glucosidase	α-glucosidase 41.85-87.13 mg/mL, acarbose= 66.31-80.20 mg/mL	α-amylase 23.47-39.63 mg/mL, acarbose= 71.37-89.00 mg/mL	inhibited α-glucosidase and moderately inhibited α-amylase.	[35]
		Palmitic acid		83.92-91.26 mg/mL, acarbose= 71.37-89.00 mg/mL	18.68-25.05, mg/mL, acarbose= 66.31-80.20 mg/mL		
		Pheophorbide A-methyl ester		53.16-75.41 mg/mL, acarbose= 71.37-89.00 mg/mL	7.23-49.84 mg/mL, acarbose= 66.31-80.20 mg/mL		
		α-Spinasterol		61.13-80.06 mg/mL, acarbose= 71.37-89.00	13.06-43.37 mg/mL, acarbose= 66.31-80.20 mg/mL		
A. hybridus		Methanol		89.92-97.10 mg/mL, acarbose= 66.31-80.20 mg/mL	5.67-27.47 mg/mL, acarbose= 66.31-80.20 mg/mL		
A. spinosus		i) chloroform fraction of a methanol extract; ii) – (14E, 18E, 22E, 26E) – methyl nonacosa-14, 18, 22, 26 tetraenoate; iii) Acarbose	α-glucosidase	α-glucosidase IC_{50} i) 8.49 μM/mL; ii) 6.52 μM/mL; iii) 15.25 μM/mL			[36]
		Ethanol	α-amylase and α-glucosidase	α-glucosidase IC_{50}. 237.06 μg/mL^{-1}, acarbose=36.98 μg/mL^{-1}	α-amylase IC_{50} 3.37 μg/mL^{-1}. The values for acarbose inhibition on α-amylase were not shown	The extract showed lower activity than acarbose in α-glucosidase. However, compared to the other plant samples, *A. spinosus* showed the most potency on α-amylase	[37]

A. viridis		Water	α-amylase	α-amylase IC_{50} 5.058±0.41 µg/mL		[38]
		Dried fruits and flowers	α-amylase	α-amylase 82.5% at 5mg/ mL. Acarbose= 99% at 1 mg/mL.		[27]
Brassica rapa	Chinese cabbage	i) licochalcone A ii) caffeic acid	α-glucosidase	α-glucosidase IC_{50} i) 118.9 µM; ii) 76.9 µM; acarbose=142 µM	Showed potent α-glucosidase inhibition	[39]
Chenopodium album	White goosefoot	Flavonoid fraction	α-amylase	α-amylase IC_{50} 122.18 ± 1.15 µg/mL; acarbose =812.83 ± 1.07 µg/mL	More efficacious than standard acarbose	[12]
		Dried fruits and flowers	α-amylase	α-amylase 32.52% at 5mg/ mL. Acarbose= 99% at 1 mg/ mL.	Showed low reduction in α-amylase activity	[27]
Cucurbita pepo	Pumpkin	i) Seed oil obtained by cavitation-accelerated aqueous enzymatic extraction (CAEE); ii) Seed oil obtained by soxhlet extraction (SE)	α-amylase	α-amylase IC_{50} i) 40.68 µg/mL; ii) 45.46 µg/mL	Showed good antidiabetic activity.	[40]
		Acetone	α-amylase	α-amylase IC_{50} 1.82 mg/mL; acarbose= 0.56 mg/mL	Suppressed α-amylase activity.	[41]
		Ethanol	α-amylase and α-glucosidase	α-glucosidase IC_{50} 144.77 µg/mL; Acarbose =35.50 µg/ mL; α-amylase IC_{50} 278.88 µg/mL; acarbose =50.01 µg/mL	Showed week α-amylase α-glucosidase inhibitory activities.	[42]
		Polysaccharide	α-amylase and α-glucosidase	α-glucosidase IC_{50} 110.32±7.08 mg/mL; acarbose= 64.04 ±2.21; α-amylase IC_{50} 103.06±1.60 mg/mL; acarbose= 71.53 ±1.67 mg/mL	Possessed α-amylase and α-glucosidase suppression activities	[43]

Table 2: Summary of antidiabetic activity of African widely consumed wild foods in animal models.

Scientific name	Common name	Extract/ Compound	Model	Dose	Duration	Results	Reference
Portulaca oleracea	Purslane	Aqueous	Alloxan-induced rats	250 mg/kg body weight (bw). Positive control, canagliflozin =10 mg/ kg bw	10 weeks	Canagliflozin reduced serum glucose levels more significantly than the *P. oleracea* aqueous extract. *P. oleracea* more effective hepatic and renal antioxidant	[44]
		Ethanol	Alloxan-induced rats	250 mg/kg bw. Positive control, canagliflozin=10 mg/ kg bw	28 days	Alleviated the impaired pancreatic acinar cells.	[45]
			Alloxan-induced rats	1. 5 ml of herb suspension/100 g bw	16 days	Exerted hypoglycaemic effects and elevated the level of serum insulin.	[46]
		Aqueous	Alloxan-induced rats	250 mg/kg	16 days	Significantly reduced Hb A1C, serum levels of glucose, TNF-α and IL-6.	[47]
		Aqueous	Alloxan-induced rats	200 and 400 mg/kg	28 days	Significantly decreased fasting blood glucose, total cholesterol and triglycerides. Improved body weight.	[48]
		Polysaccharide	Alloxan-induced rats	200 and 400 mg/kg bw	28 days	Significantly decreased concentration of fasting blood glucose (FBG), total cholesterol (TC) and triglyceride (TG). Significantly increased high-density lipoprotein cholesterol (HDLc) and serum insulin.	[49]
		Ethanol/water: 8:2	Alloxan-induced rats	50, 100 and 200 mg/kg/day	14 days	Reduced triglycerides, cholesterol and LDL.	[50]

Aqueous	db/db mice	300 mg/kg bw	10 weeks	Significantly reduced blood glucose and plasma creatinine in type 2 diabetic rats.	[51]
Aqueous	db/db mice	250 mg/kg bw. Positive control, Glibenclamide = 0.25 mg/kg bw	10 weeks	Reduced blood glucose, plasma triglyceride and systolic blood pressure.	[52]
Ethanol	db/db mice	400 mg/kg. Positive control, rosiglitazone =5 mg/kg	6 weeks	Significantly lowered blood glucose and glycosylated haemoglobin (HbA1c) levels. Significantly decreased homeostatic measure of insulin resistance.	[53]
Petroleum ether fraction	Streptozotocin-induced (STZ) diabetic mice	75 mg /kg bw	20 days	Improved liver and kidney function in diabetic rats	[54]
Ethanol	STZ-induced rats	100 mg/kg and 250 mg/kg bw. Positive control, tolbutamide =10mg/kg bw	3 weeks	Decreased lipid peroxidation that is associated with increased superoxide dismutase (SOD) and catalase (CAT).	[55]
Seeds added to the diet	Alloxan-induced rats	Basal diet supplemented with 5 and 10% aerial parts; basal diet supplemented with 5 and 10% purslane seeds	8 weeks	Increased body weight and HDL. Decreased blood glucose, TG, LDL, v-LDL levels.	[56]
Aqueous	STZ-induced rats	100, 200 and 400 mg/kg bw	4 weeks	Improved glucose, MDA, IL6, TNFa, GSH and SAT levels in the diabetic group.	[57]
*Fresh and dried extract	STZ-induced rats.		21 days	Significantly reduced ($p < 0.05$) fasting blood glucose (FBG) levels, significantly improved oral glucose tolerance test (OGTT), and insulin secretion and antioxidant activity.	[15]
Aqueous	STZ-induced rats	5, 10, 20 g/kg bw	9 weeks	Reduced the body weight, improved the impaired glucose tolerance and lipid metabolism, decreased serum free fatty acids, attenuated hyperinsulinemia and elevated insulin sensitivity.	[58]
Ethanol	STZ-induced rats	200 mg/kg and 400 mg/kg	4 weeks	Reduced islet cell necrosis and inflammatory cell infiltration in the pancreas.	[59]
Aqueous	STZ-induced rats	1 g/kg bw	4 weeks	Significantly reduced glycemia, serum total cholesterol (TC), triacylglycerols (TG), and phospholipids (PL).	[60]
Ethanol	STZ-induced rats	100 and 200 mg/kg. Positive control, metformin =10 mg/kg	28 days	Increased body weight, significantly reduced concentrations of glucose, anti-aspartate aminotransferase, alanine aminotransferase, triglycerides, total cholesterol, IL-6, IL-1β, and TNFα in serum.	[61]
Ethanol/water: 8:2	STZ-induced mice	300 mg/kg bw. Positive control, acarbose= 100 mg/kg bw	130 minutes	Lowered postprandial hyperglycaemia.	[11]

		Aqueous	STZ-induced rats	Casein diet supplemented with 1 g/kg bw of *P. oleracea*	4 weeks	Lowered glycemia and HbA1c values by 2.8- and 1.7-fold. Reduced TBARS (thiobarbituric acid reactive substances) by 54% in RBC (red blood cells) and 65% in blood plasma. Elevated SOD (superoxide dismutase) and GSH-Px (glutathione peroxidase) activities.	[62]
		Aqueous	STZ-induced rats	1% of P. *oleracea* aqueous extract	28 days	Decreased glucose and HbA1C levels. Enhanced insulin activity. Lowered plasma values of total cholesterol (TC), triacylglycerols (TG), very low- and low-density lipoprotein cholesterol (VLDL-C, LDL-C). Elevated levels of high-density lipoprotein cholesterol (HDL-C), leading to decreased atherogenic indices.	[63]
		Aqueous	STZ-induced rats	200 mg/kg	3 weeks	Significantly reduced the sugar level and lipid profile.	[64]
		Aqueous	STZ-induced rats	300 mg/kg	35 days	Significantly decreased hyperglycaemia.	[65]
		-	STZ-induced rats	5% of *P. oleracea* mixed with standard pelleted food	12 weeks	Normalised neurobehavioral deficit associated with streptozotocin such as memory deficit and anxiety.	[66]
		Hydroethanol, chloroform and carbon tetrachloride	STZ-induced rats	250 mg/kg bw. Positive control, glibenclamide = 0.25 mg/kg bw	16 days	Significantly reduced blood serum glucose. Significantly reduced LDL cholesterol levels. Chloroform and carbon tetrachloride extracts significantly reduced serum cholesterol and TG levels more than glibenclamide.	[67]
		Powder dissolved in saline	STZ-induced rats	Powder dissolved in saline	4 weeks	Lowered fasting blood glucose and glycated hemoglobin levels.	[68]
		Crude water-soluble polysaccharide	STZ-induced rats	Positive control, glyburide = 25 mg/kg bw	28 days	Significantly increased the body weight and improved glucose tolerance.	[69]
		Aqueous	Tetraoxane-induced diabetic mice	200 mg/kg. Positive control, metformin = 250 mg	21 days	Hypolipidemic effect.	[70]
Citrullus lanatus	Tsamma/ bitter melon	Aqueous	Alloxan-induced rats	200, 400 and mg/kg bw. Positive control, metformin = 100 mg/kg bw	21 days	Reduced hepatotoxicity.	[71]
		Watermelon juice	Alloxan-induced rats	500 and 1000 mg/kg bw. Positive control, metformin =200 mg/kg bw	14 days	Significantly ($p < 0.05$) lowered fasting blood glucose, serum lipid profile, glucose-6-phosphatase, lipid peroxidation, and anti-inflammatory activity.	[72]
		Watermelon juice	Alloxan-induced rats	-	-	Increase in body weight. Hypoglycemic effect, increase in increases in GSH, GPx, CAT and SOD and a decrease in MDA concentration.	[73]

	Methanol/water: 8:2	Alloxan-induced rats	i) 200 mg/kg extract. ii) 100 mg/kg caffeine iii) i + ii iv) Positive control, glybenclamide =5 mg/kg	21 days	Significantly decreased (P < 0.05) blood glucose, a significant increased sperm motility sperm count, normal sperm morphology, sperm viable cells and testosterone in plasma.	[74]
	Aqueous	Alloxan-induced rats	200, 400 and 600 mg/kg bw. Positive control, metformin =100 mg/kg bw	21 days	Significantly (p≤0.05) reduced plasma glucose, pancreatic α-amylase activity, total cholesterol, triglycerides, and lipoproteins. Significantly (p≤0.05) increased high density lipoproteins.	[75]
	Petroleum ether and ethanol	Alloxan-induced mice	150, 200, and 250 mg/kg. Positive control, glibenclamide =2 mg/kg p.o	7 days	Lowered the raised blood glucose levels significantly (P < 0.05)	[76]
	Ethanol	Alloxan-induced rats	100, 200 and 400 mg/kg. Positive control, glibenclamide =2.5 mg/kg	4 weeks	Significant decrease (P= 0.001) in blood glucose levels. Significant decreased levels of cholesterol (TC), triglycerides (TG), LDL, elevated HDL.	[77]
	Dried peels	STZ-induced rats	10, 20 and 30% dried watermelon peels	4 weeks	Significantly reduced blood glucose level. Improved serum levels of the other biomarker such as insulin and HDL, reduced glutathione (GSH), glutathione peroxidase (GPx), SOD and CAT.	[78]
	Methanol	STZ-induced rats	200, 400, and 600 mg/kg. Positive control, glibenclamide =4 mg/kg	4 weeks	Reduced fasting blood glucose, serum cholesterol, serum triglyceride, liver glycogen, and glycosylated haemoglobin.	[79]
	Methanol	STZ-induced rats	200 mg/kg bw	29 days	Significantly (P<0.05) reduced plasma glucose concentrations.	[80]
	Ethanol	STZ-induced rats	200, 400 and 600 mg/kg bw. Positive control, glibenclamide =0.5 mg/kg bw	28 days	Significantly decreased (p<0.05) glucose concentrations.	[81]
	Ethanol	STZ-induced rats	100, 400 and 800 mg/kg bw.	28 days	Significantly reduced creatine kinase (CKMB) and lactate dehydrogenase (LDH).	[82]
	Methanol	STZ-induced rats	100, 200 and 300 mg/kg	28 days	Decreased blood glucose.	[83]
	Methanol	STZ-induced rats	200, 400 and 600 mg/kg. Positive control, glibenclamide = 4 mg/kg.	4 weeks	Significantly reduced the elevated fasting blood glucose levels. Improved morphology of the pancreas.	[84]
	Ethanol	STZ-induced rats	50, 100 and 200 mg/kg	29 days	Significantly reduced serum glucose levels.	[85]
	Various globulins isolated from five Cucurbitaceae species including *C. lanatus*	Glucose tolerance test	2 g/kg bw	-	Reduced blood sugar.	[86]
	Methanol	Glucose tolerance test	100, 200, and 400 mg/kg. Positive controls, glimepiride =25 mg/kg and acarbose = 50 mg/kg	-	Hypoglycaemic effect.	[87]

Corchorus olitorius	Jew's mallow	Ethanol	Glucose tolerance test	400 mg/kg. Positive control, glibenclamide =5mg/kg	30 days	Reduced blood glucose level, prevention of oxidative damage.	[88]
		Methanol/water:8:2	-	100, 200 and 300 mg/kg	20 days	Significantly reduced body weight and serum levels of liver biomarkers, and increased haematological parameters.	[89]
		Methanol	Alloxan-induced rats	100, 250, 500 and 1000 mg/kg bw. Positive control, glibenclamide = 0.2mg/kg	14 days	Significantly ($p \leq 0.01$) lowered blood sugar levels in normoglycaemic, OGTT and diabetic rats.	[90]
		Hexane, chloroform, ethyl acetate	Alloxan-induced rats	250 and 500 mg/kg bw. Positive control, glibenclamide =0.2 mg/kg	-	Hypoglycaemic activity.	[91]
		Aqueous	Alloxan-induced rats	400mg/kg bw	28 days	Reduced serum blood glucose level and other biochemical parameters.	[92]
		Stearic acid ethyl ester	Alloxan-induced rats	230 mg/kg. Positive control, glibenclamide = 0.2 mg/kg	-	Reduced fasting blood sugar level. Results were comparable with a reference drug, glibenclamide.	[93]
			STZ-induced rats	10% *C. olitorius*	4 weeks	Significantly decreased serum glucose levels	[94]
		-	STZ-induced rats	+High fat diet supplemented with 10% of jute leaf. Positive control, acarbose=50mg/kg bw.	30 days	Reversed blood glucose, α-amylase, α-glucosidase, angiotensin-1-converting enzyme activities, lipid peroxidation in pancreas, total cholesterol and triglyceride levels in diabetic rats.	[95]
		Ethanol	STZ-induced rats	1.25 g/kg bw. Positive control, glibenclamide =20 mg/kg bw	28 days	Significantly reduced serum glucose level. No significant improvement in lipid profile.	[96]
		-	STZ-induced rats	100 mg/g jute leaf-supplemented diet	30 days	Significantly ($p < 0.05$) reversed decreased hepatic δ-ALAD activity.	[97]
		Ethanol	STZ-induced rats	250 mg/kg. Positive control, protocatechuic acid=20 mg/kg	3 weeks	Significantly lowered blood glucose levels. Seminiferous tubule degenerations were prevented, and apoptotic cell numbers were reduced.	[98]
		Methanol	STZ-induced rats	100 and 200 mg/kg	21 days	Significantly (<0.001) decreased blood glucose and cholesterol levels.	[99]
		Ethanol, chloroform and aqueous fractions	STZ-induced rats	50 and 100 mg/kg. Positive control, gliclazide =10 mg/kg	14 days	Decreased serum glucose level. Improved the lipid profile, decreased liver damage markers, and significantly increased the number, size, and density of functioning β-cells.	[100]
		C. olitorius powder	Long-Evans Tokushima Otsuka (LETO) rats (controls) and Otsuka Long-Evans Tokushima Fatty (OLETF) rats	LETO rats were fed with a normal diet containing (336 kcal energy, 8.6g moisture, 18.1 g protein, 3.8 g fat, 5.8 g dietary fibre 6.3 g ash (1.06 g calcium). OLETF rats consumed 97% of the normal diet and 3% dry powder of *C. olitorius*.	8 weeks	There were no significant differences in plasma glucose and serum insulin observed between *C. olitorius* fed OLETF and LETO rats. There were no significant differences in serum triglyceride, total serum cholesterol, total liver cholesterol, and total liver fat among the groups.	[60]

		Aqueous	Alloxan-induced mice	50, 100 and 150 mg/kg. Positive control, insulin =1 IU/kg bw	30 days	Reduced the blood glucose levels.	[101]
		Aqueous	Alloxan-induced rats	200 mg/kg, 400 mg/kg and 800 mg/kg. Positive control, glibenclamide =0.5 mg/kg)	4 weeks	Reduced glucose levels.	[102]
		Ethanol/water: 85:15	Alloxan-induced rats	500 mg/kg bw. Positive control, tolbutamide as a reference =60 mg/kg	-	Significantly reduced the hyperglycaemia.	[103]
Bidens pilosa	Black jack	Methanol extract, cytopiloyne	db/db mice	Extract=1000 mg/kg, compound =250 and 500 mg/kg. Positive control, glimepiride =1 mg/kg bw	33 days	Showed higher glucose-lowering and insulin-releasing activities. In addition, the extract and compound significantly reduced the percentage of the glycosylated hemoglobin A1c.	[104]
		Aqueous extract. 3:2 mixture of 2-beta-D-glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-+ ++triyne (1) and 3-beta-D-glucopyranosyloxy-1-hydroxy-6(E)-tetradecene-8,10,1 2-triyne.	db/db mice	Compound = 250 and 500 mg/kg. Extract = 1000 mg/kg. Positive control, metformin =250 mg/kg	-	Caused a significant drop in blood glucose.	[105]
		Aqueous	STZ-induced rats	10, 50 and 250 mg/kg bw. Positive control, glibenclamide =2.5 mg/kg	28 days	Decreased blood glucose levels, significantly improved glucose tolerance.	[106]
		Methanol	STZ-induced rats	100, 200 and 400 mg/kg. 200 mg/kg of chromium picolinate and extract 100 mg/dL.	28 days	Showed a decrease in blood sugar levels.	[107]
		Butanol fraction	Non obese diabetic mice (NOD)	3 and 10 mg/kg	18 weeks	Prevented mice from hyperglycemia and hypoinsulinemia.	[108]
		Butanol fraction	Non obese diabetic mice (NOD)	10 mg/kg extract	18 weeks	Maintain the normal morphology of pancreatic β islets. Furthermore, treatment of NOD mice with the butanol fraction of *B. pilosa* inhibited β-cell death and leukocyte infiltration.	[109]
Amaranthus spp.							
A. caudatus		Hydroethanolic	Goto-Kakizaki (GK)	1000 and 2000 mg/kg bw	21 days	Improved glucose tolerance, increased serum insulin levels.	[110]
	Pigweed	-	STZ-induced rats	250 and 500 mg/kg bw	21 days	Reduced blood glucose, increased activities of both enzymatic and non-enzymatic antioxidants.	[111]
A. spinosus		Methanol	STZ-induced rats	200 and 400 mg/kg	-	Showed significant antidiabetic and anticholesterolemic activity (P<0.01).	[112]
		Methanol	STZ-induced rats	200 and 400 mg/kg	21 days	Antidiabetic and hypolipidemic activities.	[113]
		Methanol	STZ-induced rats	250 and 500 mg/kg. Positive control, glibenclamide =500 µg/kg	15 days	Significantly exhibited control of blood glucose level. Accelerated spermatogenesis by increasing the sperm count and accessory sex organ weights.	[57]

	Methanol	Glucose tolerance test	50 and 500 mg/kg bw. Positive control, glibenclamide = at 10 mg/kg bw	-	Antihyperglycemic activity.	[114]
	Hydroethanolic	Oral glucose tolerance test	125, 250 and 500 mg/kg bw. Positive control, glibenclamide = 0.6 mg/kg bw	180 minutes	Showed a significant ($p < 0.001$) decrease in blood glucose levels.	[115]
	Ethanol	Alloxan-induced rats	150, 300 and 450 mg/kg bw. Positive controls, glibenclamide = 600 µg/kg bw and metformin = 500 mg/kg bw	30 days	Significantly decreased ($p<0.01$) plasma glucose levels, hepatic glucose-6-phophatase activity and increased hepatic glycogen content ($p<0.01$) with a concurrent increase in hexokinase activity ($p<0.01$). Higher doses significantly reduced plasma and hepatic lipids, urea, creatinine levels and lipid peroxidation.	[116]
A. tricolor	Methanol	Glucose tolerance test	200 and 400 mg/kg bw. Positive control, glibenclamide =10 mg/kg bw	2 hours	Reduced blood glucose	[117]
	Aqueous	Alloxan-induced rats	3 ml/kg/day bw. Positive control, glibenclamide =10 mg/kg	14 days	Significantly reduced blood glucose and cholesterol levels.	[118]
	Aqueous	Alloxan-induced rats	200 and 400 mg/kg bw	12 hours	Lowered serum glucose, serum triglyceride, total cholesterol, low density lipoprotein, and very low density lipoprotein but increased ($p < 0.05$) high density lipoproteins.	[119]
	Methanol	Alloxan-induced rats	400 mg/kg bw	7 days	Improved in body weight	[120]
	Methanol	Alloxan-induced rats	200 and 400 mg/kg. Positive control, glibenclamide =10 mg/kg	15 days	Significantly reduced blood glucose and lipid profiles.	[121]
A. viridis	Methanol	STZ-induced rats	200 and 400 mg/kg bw	21 days	Significantly increased body weight, decreased blood glucose, total cholesterol and serum triglycerides.	[122]
	Aqueous	STZ-induced rats	100, 200 and 400 mg/kg bw	30 days	Lowered blood glucose levels in a dose-dependent manner, modulated lipid profile changes.	[123]
	Methanol	Glucose tolerance test	50, 100, 200 and 400 mg/kg bw. Positive control, glibenclamide =10 mg/kg bw	120 minutes	Demonstrated dose-dependent significant antihyperglycemic activity.	[124]
	Aqueous	Alloxan-induced rats	200 mg/kg bw	24 hours	Significant ($p < 0.05$) reductions in the mean fasting blood glucose.	[125]
				12 hours		[119]
	Ethanol	STZ-induced rats	200 and 400 mg/kg	14 days	Caused a significant ($p < 0.001$) reduction in blood glucose levels. Decreased in malondialdehyde protein, increase in superoxide dismutase protein, catalase protein and reduced glutathione protein.	[126]

A. hybridus		Ethanol	STZ-induced rats	100 and 200 mg/kg bw	30 days	Significantly ($p < 0.05$) reduced the serum levels of glucose, total cholesterol and triglycerides.	[127]
		Ethanol	STZ-induced rats	200 and 400 mg/kg	14 days	Reduced elevations in the serum levels of creatinine, urea and uric acid, and urine levels of total proteins and albumin. The histopathological examination of kidney in drug treated rats shows significant protective effect against STZ oxidative stress.	[128]
Brassica rapa	Chinese cabbage	Ethanol	Alloxan-induced rats	10, 15, and 20 mg/kg bw	30 days	Significantly ($p<0.05$) reduced blood glucose and malondialdehyde levels	[129]
		Ethanol	db/db mice	0.26 g/100 g diet. Positive control, rosiglitazone =0.005 g/100 g diet	5 weeks	Improved hepatic glucose and lipid metabolism.	[130]
Cucurbita pepo	Pumpkin	Aqueous	STZ-induced rats	100 and 400 mg/kg. Positive control, metformin =50 mg/kg	4 weeks	Significantly improved antihyperglycemic activity. Effectively reduced liver enzyme increase and histological damage.	[131]
		Ethanol	STZ-induced rats	0.5, 2.0 and 5.0 mg/kg bw. Positive control = glibenclamide =125 mg/kg bw	4 weeks	Decreased the level of blood glucose. In addition, histological studies showed a restorative effect.	[132]
		Aqueous	Triton hyperlipidemia induced rats	200 and 400 mg/kg bw. Positive control, atorvastatin =10mg/kg bw	10 days	Prevented the rise of plasma total cholesterol. The extract also significantly($p<0.05$) decreased LDL cholesterol and triglyceride levels in hyperlipidemic.	[133]
		Ethanol	Alloxan-induced rats	200 mg/kg	8 weeks	Significantly decreased the levels of serum biomarkers of hepatic injury in the diabetic rats	[134]
		-	Alloxan-induced rats	-	-	Reduced the elevated levels of the plasma enzymes produced by the induction of diabetes	[135]
		-	Alloxan-induced rats	100% wheat flour and fortified cake with 10% and 20% zucchini flowers powder	30 days	Significant increased HDL-C accompanied by a significant decrease in total cholesterol, TG, LDL-C and VLDL-C. Restored acetylcholinesterase (AChE), catalase (CAT) and glutathione (GSH) activities which were lowered in brain of diabetic animal.	[136]
		Petroleum ether and hydro-alcoholic extract	STZ-induced rats	100, 200, and 400 mg/kg	45 days	Significantly increased body weight, lowered blood glucose levels, and ameliorated kidney hypertrophy index. Decreased the levels of creatinine, blood urea nitrogen, total cholesterol, triglycerides, AGEs and albumin in urine.	[137]

		Ethanol	-	10% extract of C. pepo leaves +90% growers mash.	18 days	Showed no significant differences regarding lipid levels. Although the difference was statistically insignificant (P=0.068), there was a marked increase in the HDL level of the test group.	[138]
		Polysaccharide (PP-PE) obtained by hot-water extraction from *Cucurbita pepo*	Alloxan-induced rats	100 mg/kg. Positive control, chlorpropamide = 100 mg/kg	7 days	Decreased blood glucose levels.	[43]
		Ethanol	Alloxan-induced rats	250 and 500 mg/kg bw	15 days	Nearly reversed most of the changes induced by alloxan such as serum glucose and hepatic lipid peroxidation	[139]
		-	Alloxan-induced rats	1 and 2 g/kg	4 weeks	Significant decreased levels of liver enzymes (ALT, AST, ALP) which were high in untreated diabetic rats.	[140]
		Tocopherol fraction	PX-407-induced rats	2 and 5g/kg	12 weeks	Showed a significant improvement in glycemia, insulinemia, and lipid dysmetabolism	[141]
Chenopodium album	White goosefoot	Flavonoid fraction (CAFF), tannin fraction (CATF), alkaloid fraction (CAAF)	STZ-induced rats	250 and 500 mg/kg	14 days	Significant decreased glucose, cholesterol, and triglyceride levels.	[12]
		Methanol	STZ-induced rats	200, 350 and 500 mg/kg bw. Positive control, glibenclamide =10 mg/kg bw	28 days	Normalised plasma lipid status and decreased cholesterol, triglyceride, and LDL levels.	[142]
		Methanol	Alloxan-induced rats	200 and 400 mg/kg. Positive control, metformin =25 mg/kg	7 days	Significantly (p<0.05) reduced the serum glucose, elevated dyslipidemia, SGOT and SGPT levels.	[143]
Cleome gynandra	Spider flower	Ethanol	STZ-induced rats	250 and 500 mg/kg	8 days	Produced a dose-dependent fall in fasting blood glucose. Moreover, serum lipid levels were restored to near normal levels.	[144]
		Methanol	STZ-induced rats	400 mg/kg bw. Positive control, glibenclamide =20 mg/kg bw	21 days	Significantly reduced the levels of AST, ALT, ALP, total bilirubin, urea and creatinine.	[145]
		Ethanol	Alloxan-induced rats	200 mg/kg	14 days	Elevated HDL and reduced triglycerides, total cholesterol, LDL and VLDL.	[146]

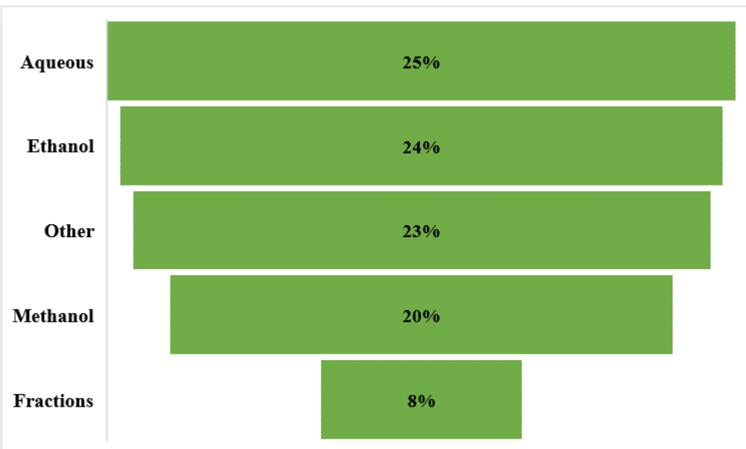

Figure 1: Extracted and fractionated wild antidiabetic plants in South Africa

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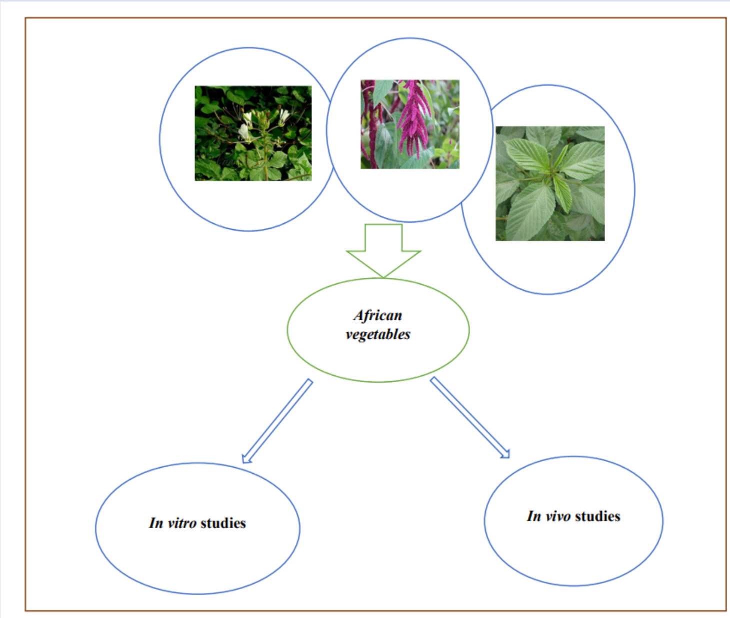
GRAPHICAL ABSTRACT



ABOUT AUTHORS

Nolitha Nkobole: Lecturer in the Department of Agriculture and Animal Health, University of South Africa.

Lavhelesani R. Managa: Research Specialist at the Human Sciences Research Council.

Gerhard Prinsloo: Professor in the Department of Agriculture and Animal Health, University of South Africa.

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