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Invivo effects of specioside on Diabetic Neuropathy

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Abstract

Diabetic neuropathic pain is a prevalent, severe, and incapacitating condition that poses a huge obstacle to medical care. There are numerous medications on the market, but no effective conventional treatments exist for neuropathic pain. In medical research, herbal formulation has received increased interest lately. Specioside is one of the isolated compound from African traditional medicines is *Kigelia africana* which exhibits a wide range of therapeutic value and has a lot of scientific interest due to its wide range of pharmacological properties to treat illnesses. Additionally, phytoconstituents from the plant are known to exist, that was found in n-hexane, chloroform, ethanol, and ethyl acetate aqueous extracts including alkaloids, glycosides, phenols, flavonoids, and other phytoconstituent are known as speciocide.This speciocide emerging antidiabetic effect interconnection with diabetic secondary complications of diabetic neuropathy, retinopathy, and nephropathy. Our study mainly focused on the Invitro inhibitory assay of enzyme α-amylase hydrolyzing the glycosidic linkages in carbohydrates to produce oligosaccharides, which are broken down

into monosaccharide glucose by α-glucosidase. Aldose reductase is responsible for the NADP-dependent conversion of glucose to sorbitol, potentially increasing the post-prandial glucose level. These enzyme actions are blocked by speciocide, which might reduce diabetic neuropathy pain.

Keywords: Diabetic neuropathy, *K.africina*, Speciocode, Alpha-amylase, Alpha-glycosidase, Aldoreductase

Introduction

Diabetic neuropathy is a type of nerve damage that can occur if you have diabetes. High blood sugar (glucose) levels can injure nerves throughout the body. Diabetic neuropathy mostly often damages the nerves in the legs and feet (Kern et al., 2009). Diabetic neuropathic pain (DNP) is characterized by tingling, burning, sharp, shooting, and lancinating or even electric shock sensations. Diabetic neuropathy is the most frequent microvascular problem (weakening of the small blood vessels) seen in people with diabetes (Bondar et al., 2021). After 20 years of disease progression, this consequence affects over 50% of DM patients significantly lowering their quality of life due to the characteristic persistent pain in their lower limbs and it is still a significant contributor to morbidity. It is a known risk factor for falls caused by balance difficulties and diabetic foot syndrome, particularly in elder patients. Additionally linked to a higher risk of infection and amputation. Furthermore, the DNP could lead to problems with the digestive system, urinary tract, heart, and blood arteries (Román-Pintos et al., 2016). According to the International Diabetes Federation reports diabetes is one of the main causes of neuropathy, recently affecting 382 million individuals worldwide more than 90% of individuals have distal symmetrical polyneuropathy (DSPN), the most prevalent clinical type of diabetic neuropathy (Schreiber et al., 2015). The toes and the distal foot are typically affected by DSPN, but it gradually spreads proximally to include the feet and legs in the distribution of stockings. Moreover, a progressive loss of nerve fibers affecting the somatic and autonomic divisions is another characteristic; as a result, diabetic retinopathy and nephropathy may develop. after meals, blood glucose levels might remain elevated, which is referred to as postprandial hyperglycemia (PPHG) (Tesfaye et al., 2013). The enzyme α-amylase hydrolyzes the glycosidic linkages in carbohydrates to produce oligosaccharides, which are subsequently broken down into monosaccharide glucose by α-glucosidase (Ogunyemi et al., 2022). Aldose reductase is responsible for the NADP-dependent conversion of glucose to sorbitol, which causes an excessive build-up of intracellular ROS in diabetic patients with other organs heart, vascular, neurons, eyes, and kidney tissues illness (Comakli et al., 2022).Aldose reductase is a key player in the pathophysiology of problems related to diabetes. Many experimental findings showing that blocking Aldose reductase reduces or delays hyperglycemic damage in a variety of animal models of diabetes have led to the proposal that aldose reductase is one of the main mediators of secondary diabetic problems (Patel et al., 2012). Under hyperglycemic circumstances, it has been suggested that increased glucose flow through aldose reductase would cause increased osmotic and oxidative stress Consequently, a sequence of metabolic alterations is triggered, resulting in extensive cellular damage, modified intracellular communication, and severe malfunctioning in tissues and subcellular organelles such as mitochondria and cell death (Sarikaya et al., 2020). Many herbal extracts from medicinal plant sources that have been shown to have antidiabetic

effects are a good way to supplement existing treatments in developing nations they are regarded as significant plant sources for antidiabetic medications, alpha-amylase, alpha-glucosidase, and aldose reductase inhibitors, and preventative nutraceuticals (E. N, Ezeanyika, et al., 2019). They may also be used as an oral medication to decrease blood glucose spikes after meals in people with diabetes and metabolic syndrome. Recently, antidiabetic herbs have been found to have an activity against alpha-amylase. *Kigelia africana* Benth is one such plant that has been utilized in African traditional medicine to treat diabetic problems (Osman et al., 2017). *Kigelia africana* (Lam) belongs to the family of Bignoniaceae. The fruit, leaves, stem, wood, and flower of *K. africana* have been used in traditional medicine to treat a variety of conditions, including rheumatism, diabetes, bacterial infections, fungal infections, psoriasis, eczema, dysentery, malaria, pneumonia, ulcers, and gynecological disorders (Arhikv et al., 2014). It has also been used as an anti-inflammatory and to treat cancer. The roots, the wood, and the leaves have been found to contain nigellone, vitriolic acid, kigelia, iridoids, luteolin, and 6-hydroxy luteolin (Oyelami et al., 2012). *K. africana* fruit was found to contain 2,4-di-tert-butyl-phenol, a chemical linked to diabetes mellitus for the first time that may be utilized as a novel therapy approach that would potentially block the α-amylase enzyme which delays the glucose absorption and further reducing fasting blood glucose levels. Another study on the α-amylase inhibitory impact of different solvent extracts of the leaves (acetone, ethanol, chloroform, and water) found a significant decrease in enzyme activity (Adefegha and Oboh, 2012). fruit extract of *K. africana* demonstrated a significant proportion of flavonoids, glycosides, alkaloids, and terpenoids among other components. These plant-based components can lower blood glucose levels. Especially, Aldose reductase is the main enzyme in the polyol pathway, and extracts from ***K. africana*** suppress its enzyme activity (Muyenga et al., 2023). there is a dearth of scientific data regarding the plant's anti-diabetic neuropathy qualities. This study aims to investigate the influence of hydrolyzing enzyme activity as well as polyol enzyme activity interconnected with diabetic secondary complications. ***K.africina*** ethanolic fruit may reduce the diabetic neuropathy problem.

Materials and Method

Alpha-amylase inhibitory assay

Alpha-amylase inhibition was determined by quantifying the amount of maltose liberated during the experiment. Different concentrations of speciocide (10, 20, 30, 40, 50 µL) were pre-incubated with 100 µL of α-amylase solution (1 U/mL) at room temperature for 30 minutes. 100 µL of starch solution (1% w/v) was further added to it and the mixture was incubated at room temperature for 10 minutes. 100 µL of 96 mM (3, 5- dinitro salicylic acid solution) DNSA reagent was added to it to stop the reaction and the solution was heated in a water bath for 5 minutes. Control was maintained where the equal quantity of enzyme extract was replaced by sodium phosphate buffer maintained at a pH value of 6.9. Reading was measured at 540 nm. The experiment was performed in triplicate. Acarbose was used as a positive control (Agarwal et al., 2018).

% inhibition was calculated using the formulae-

$$\%\ \text{inhibition} = \frac{C - T}{C} * 100$$

Where, C= control, T= test sample.

Evaluation of the Alpha-Glucosidase Enzyme Inhibition

The speciocide at concentrations of 10,20,30,40,50 µg/ml was mixed with starch substrate solution (2% w/v maltose or sucrose) in the presence of 0.2 M Tris buffer at pH 8.0 and incubated for 5 min at 37° C. Subsequently, 1 ml of the alpha-glucosidase enzyme (1 U/ml) was added and incubated at 35° C for 40 min. The reaction was terminated with the addition of 2 ml of 6 N HCl. acarbose was used as a standard control. The col our intensity was measured at 540 nm using an ELISA reader, and alpha-glucosidase enzyme inhibition (I%) was calculated using the formula below: I% = 100 − As − Ab Ac − Ab × 100,

ð3Þ where I% is the inhibition percentage and As, Ab, and Ac are the average absorbance of the speciocide, blank, and control (acarbose), respectively (Nabatanzi et al., 2020).

Evaluation of the Aldose reductase Enzyme Inhibition

The enzyme aldose reductase reduces DL-glyceraldehyde as a substrate to glycerol during the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to NADP+, which is the basis of this procedure. A spectrophotometer was used to measure the oxidation of NADPH at 340 nm spectrophotometrically. In this investigation, the reaction mixture was supplemented with speciocide of *Kiegelia africana* in different concentrations (10, 20, 30, 40, and 50 µg/ml), in the sequence shown in the table. Each reaction cuvette was exposed to an aldose reductase enzyme activity test for five minutes. Before the addition of the substrate, absorbance was measured at 340 nm. Glyceraldehyde was then added to the cuvette, and after three minutes of incubation, the absorbance decreased and was measured at 340 nm once more. To find the aldose reductase inhibitor activity, repeat the same procedure with the addition of plant extract. The test sample consisted of all the components of the reaction mixture of standard along with 200 mL of different concentrations of inhibitor sample solutions, individually. These samples were read against the control. The reaction was initiated by the addition of 200 mL of DL-glyceraldehyde, and absorbance was measured at 340 nm using a UV–visible spectrophotometer (Veeresham et al., 2013).

% of Inhibition was calculated using the formulae,

$$\text{ARI\%} = \left\{ \frac{\Delta A\ \frac{\text{Sample}}{\text{Min}} - \Delta A\ \frac{\text{Blank}}{\text{Min}}}{\Delta A\ \frac{\text{Standard}}{\text{Min}} - \Delta A\ \frac{\text{Blank}}{\text{Min}}} \right\} \times 100$$

Statistical analysis

Every examined data set was presented as mean ± standard deviation (SD). There was statistical analysis carried out. utilizing Graph Prism pad software version 8.0.1. Disparities

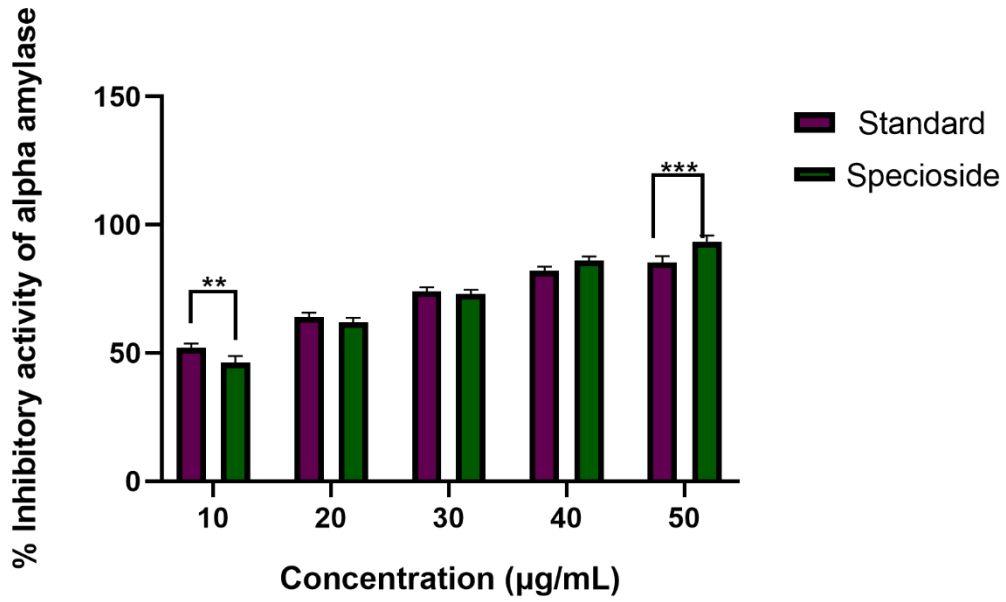
statistical significance between the means was examined using either a one-way analysis of variance (ANOVA) or a two-way ANOVA and Sidak post hoc analysis revealed significant differences to be***p<0.001, **p<0.01, and *p<0.05.

Results

In-vitro Alpha-amylase inhibitor activity

The present study employed the in-vitro approach to assess the inhibitory effect of Speciocide of *Kigelia africana* and standard (Acarbose) on α-amylase enzymes. Various concentrations of 10, 20, 30, 40, and 50 µg/mL *of Kigelia africana* ethanolic extract and standard medication demonstrated α-amylase inhibitory activity, with statistically significant differences as ***p<0.001, **p<0.01, and *p<0.05.

Alpha amylase					
Concentration	10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
Speciocide	45.3	62	73	74	86
Standard (Acarbose)	52	64	74	82	85.3

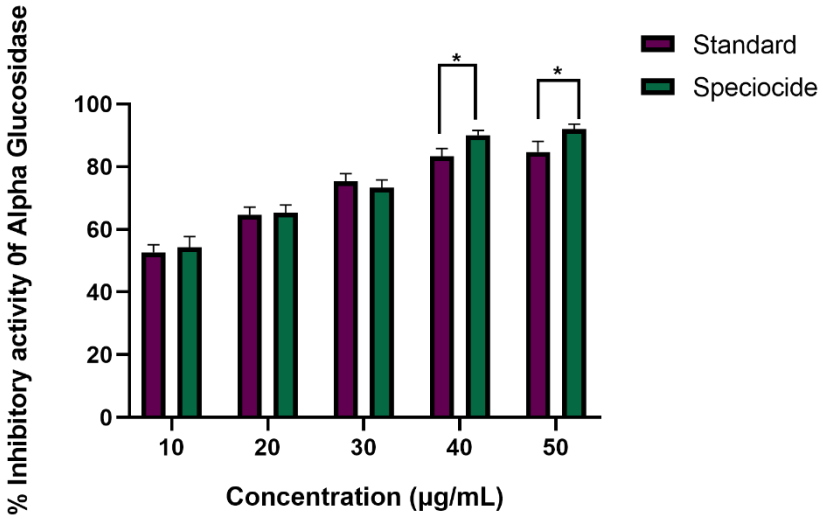


The Graphical representation shows the enzyme inhibitory action of alpha-amylase, which in the different concentrations of speciocide of *K. africana* with the standard (Acarbose) at 10 and 40 µg/mL exhibited a statistically significant difference (**p<0.01), (***p<0.001)

In-vitro Alpha-glycosidase inhibitor activity

The present study employed the in-vitro approach to assess the inhibitory effect of speciocide of *Kigelia africana* and standard (Acarbose) on α-glycosidase enzymes. Various concentrations of 10, 20, 30, 40, and 50 µg/mL of speciocide of *K.africana* and standard medication (Acarbose) demonstrated α-glycosidase inhibitory activity, with statistically significant differences as ***p<0.001, **p<0.01, and *p<0.05

Alpha glucosidase					
Concerntration	10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
Speciocide	54.3	65.3	73.3	80.3	83
Standard (Acarbose)	52.6	64.6	75.3	83.3	84.6

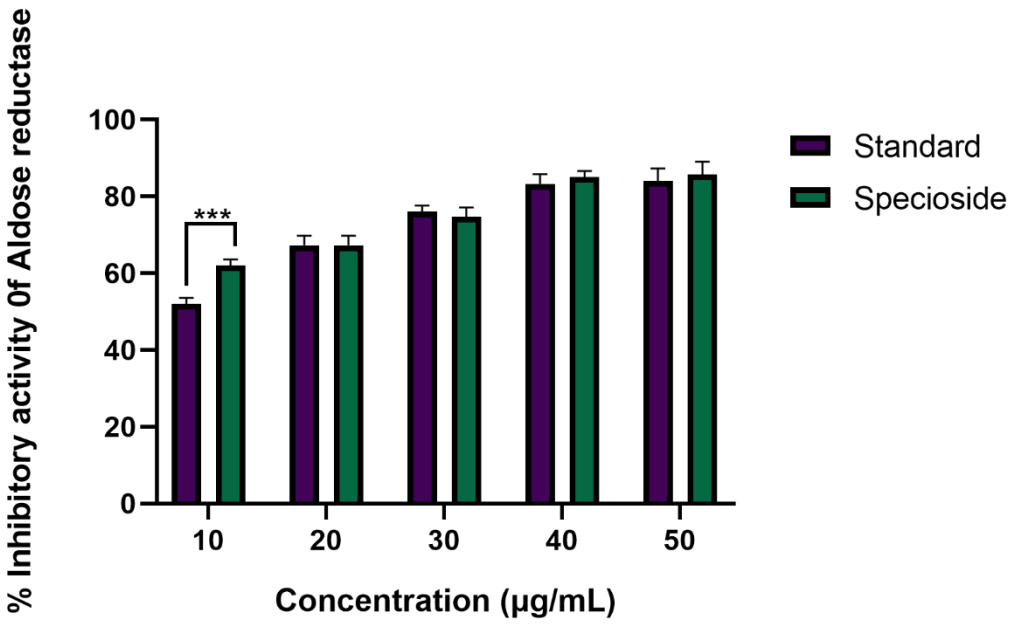


The Graphical representation shows the enzyme inhibitory action of alpha-glycosidase, Different concentrations of speciocide of K. africana with the standard (Acarbose) at 40 and 50 µg/mL exhibited a statistically significant difference (*p<0.05).

In-vitro Aldose reductase inhibitor activity

The present study employed the in-vitro approach to assessing the inhibitory effect of speciocide of *Kigelia africana* and standard (Acarbose) on aldose reductase enzymes. Various concentrations of 10, 20, 30, 40, and 50 µg/mL *of* Speciocide *Kigelia africana* and standard medication (Acarbose) demonstrated aldose reductase inhibitory activity, with statistically significant differences as ***p<0.001, **p<0.01, and *p<0.05.

Aldose reductase					
Concerntration	10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
Speciocide	62	67.3	74.6	85	85.6
Standard (sorbnil)	52	67.3	76	83.3	84



The Graphical representation shows the enzyme inhibitory action of aldose reductase, Different concentrations of speciocide of *K. africana* with the standard (Acarbose) at 10 µg/mL exhibited a statistically significant difference (***$p<0.001$).

Discussion

Diabetes-related neuropathy is a complicated and dangerous condition linked to a lifestyle that is rapidly getting worse and may soon turn into a health crisis(Dewanjee et al., 2018). Excessive glucose intake, obesity, physical inactivity, and environmental variables all raise blood glucose levels, which then damage the brain's peripheral nerves and result in diabetic neuropathy (Manson et al., 1992). It is usually considered moderate to severe and often worse at night, causing sleeping disturbances (Quattrini and Tesfaye, 2003). The pain can be constant and accompanied by cutaneous allodynia, which can substantially affect the quality of life of the patient. it may cause discomfort that could linked to depression and be the cause of a person's retreat from social and leisure activities (Gore et al., 2005). Diabetic neuropathy Patients with long-term Severe gastrointestinal symptoms, such as postprandial fullness, nausea, vomiting, bloating, early satiety, and stomach discomfort, heart symptoms like arrhythmia and heart failure, Genitourinary dysfunction correlated with diabetic autonomic neuropathy including diabetic bladder dysfunction, sexual dysfunction, and recurrent urinary tract infections(Kern et al., 2009). Diabetic neuropathy can cause excruciating pain and incapacity in many individuals. In addition, DNP is linked to several other risk factors, including aging, long-term diabetes, drinking alcohol, and smoking cigarettes. There is ambiguity about the pathophysiology of Diabetic neuropathy (Zelman et al., 2003). Many theories have been proposed to explain the pain associated with diabetic peripheral neuropathy encompasses sensory, motor, and autonomic neuropathy (Jahantigh Akbari et al., 2020) . Implicated causes of peripheral nerve damage include oxidate stress damage, accumulation of sorbitol, advanced glycosylation end products, and a disturbance of

hexosamine, protein kinase C, and polymerase pathways. Neurovascular impairment with poor repair processes and endothelial dysfunction also have been implicated. altered expression of sodium and calcium channels, glial cell activation in metabolic and autoimmune disorders, and more recently contributed to central pain mechanisms such as increased thalamic vascularity and imbalance of the facilitatory/inhibitory descending pathways (Tomic et al., 2022).The enzymes alpha-amylase and alpha-glucosidase are important therapeutic targets used in developing various synthetic medications, including miglitol, voglidose, acarbose, alrestsin, and sorbinil (Kajaria et al., 2013). Many herbal extracts from medicinal plant sources that have been shown to have antidiabetic effects are a good way to supplement existing treatments in developing nations they are regarded as significant plant sources for antidiabetic medications, alpha-amylase, alpha-glucosidase and aldose reductase inhibitors, and preventative nutraceuticals. They may also be used as an oral medication to decrease blood glucose spikes after meals in people with diabetes and metabolic syndrome (Derosa and Maffioli, 2012). Previous research on the Kigelia pinnata belonging to the Bignoniaceae family demonstrated hypoglycemic qualities in animal models (Houghton, 2002)**.** ***Kigelia africana*** possesses antioxidant properties such as caffeic acid and its derivatives with strong antioxidant potentials are another reason was decided that the ***K. africana*** plant has antidiabetic properties (Costa et al., 2017). Furthermore, it has been discovered that several substances have antioxidant and antidiabetic properties, including hydroxymethyl furfural, eugenol, trans ferulic acid, 2,4-dibutyl tetra phenol, derivatives of cinnamic acid, pyridine, and pyrimidine derivatives (Fagbohun et al., 2020). These substances have shown promise in improving pancreatic beta-cell function and glucose uptake while also inhibiting the actions of alpha-amylase and alpha-glucosidase. The enzyme α-glucosidase, which is membrane-bound and situated at the epithelium of the small intestine, catalyzes the conversion of glucose from disaccharides to monosaccharides. For type 2 diabetes mellitus, α-glucosidase inhibitors regulate blood sugar levels (Blaak et al., 2012). α-glucosidase inhibitors are typically taken with meals because they slow down the conversion of complex carbohydrates to glucose, delaying the absorption of glucose and lowering postprandial blood sugar levels. Sorbitol builds up inside cells due to an enhanced glucose flow through the polyol pathway. A build-up of this impermeable sugar in cells, particularly in the eye lenses and nerves, causes cellular edema, osmotic stress, redox imbalance, antioxidant depletion in water-soluble cells, and increased vulnerability to oxidative damage (Williams et al., 2012). This pathophysiological condition of diabetes mellitus is interconnected with long-term complications. carbohydrate-hydrolyzing enzymes α-amylase and α-glucosidase cause postprandial hyperglycemia by their actions. Postprandial hyperglycemia is caused by α-glucosidase's enzymatic conversion of disaccharides to monosaccharides, which is catalyzed by α-amylase's hydrolysis of 1, 4-glycosidic bonds of polysaccharides (starch, glycogen). These enzyme inhibitors help slow the digestion of carbohydrates and regulate hyperglycemia, lowering postprandial plasma glucose levels (Roig-Zamboni et al., 2017). Aldose reductase inhibition plays a larger role in the polyol pathway, which is linked to diabetic microvascular problems. Due to their rapid sorbitol metabolism by sorbitol dehydrogenase and excellent penetration across cell membranes, phytoconstious as Aldose reductase inhibitors are currently the most often utilized oral medications (Dewanjee et al., 2011). They are crucial for managing diabetes complications, including cataracts, retinopathy, and neuropathy. Ethyl acetate and chloroform extraction of ***K.africana*** fruit fractions showing the reduction in the activity of alpha-glucosidase activity.

People with diabetes see a decrease in postprandial glucose levels**.,** The present study results show that ethanolic fruit extract of K. africana efficiently inhibited all three of the enzymes in vitro and that there was a dose-dependent rise in the percentage of inhibitory action against the enzymes(Locvv and Kaszkin, 2002). Based on the collected results, the plant isolate was found to exhibit a statistically significant difference in the percentage of speciocide inhibition and the standard drug treatments.

Conclusion

Specioside compound isolated from *K. Africana* fruit extract is a traditional medicinal plant used widely in complementary and alternative medicine to treat diabetes, associated with secondary issues of diabetic neuropathy. Its use has been supported by numerous established scientific lines of evidence. The present in vitro study demonstrated that the ethanolic fruit extract of *K. Africana* may suppress the activities of the hydrolytic enzymes α-amylase and α-glucosidase, as well as the polyol enzyme aldose reductase, resulting in a considerable reduction of blood glucose levels. It might mitigate the effects and manifestations of diabetic neuropathy. More research is needed to turn this natural supply of phytochemicals substance into an oral medicine with anti-diabetic effects.

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