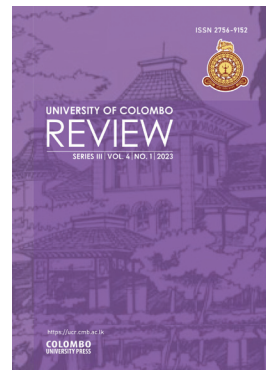


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Pumpkin seeds and leaves as an alternative medicine for the treatment of hyperglycemia

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to unhealthy dietary patterns, sedentary lifestyle behavior, and obesity. Among the two types of diabetes, type 2 is the most common in the world and the drugs used to treat hyperglycemia in type 2 DM cause adverse side effects. Hence, it is important to search for an effective natural anti-diabetic treatment to combat hyperglycemia and its complications in diabetic patients. Among the different herbal plants, pumpkin is very popular in terms of reducing blood glucose levels. Pumpkin is a popular vegetable cultivated all over the world and a rich source of bioactive compounds including phenolic compounds, unsaturated fatty acids, vitamin E and carotenoids. Currently, considerable attention is given to the seeds, leaves, and flesh of pumpkins due to their nutritional value and health benefits. However, this article focuses on the potency of pumpkin seeds and leaves to treat hyperglycemia.

KEYWORDS:

Pumpkin seeds; Pumpkin leaves; Family Cucurbitaceae; Bioactive compounds; Diabetes; Hyperglycemia.

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Introduction

Diabetes Mellitus (DM) is a rapidly expanding metabolic condition worldwide, characterized by elevated blood sugar levels. Although there are many pathological processes associated with diabetes, it is often divided into two categories as type 1 and type 2 (Arzoo et al., 2018). Type 1 DM is a condition where the body's immune system erroneously targets and eliminates the β cells in the pancreas, resulting in the disruption of insulin synthesis which is necessary for regulating blood sugar levels. In type 2 diabetes, the cellular uptake of glucose is lower in response to the normal insulin level (Adams et al., 2014). Type 2 DM, which is the more prevalent of the two types is primarily attributed to an unhealthy eating regimen, a lack of physical activity and being overweight (Zaccardi et al., 2016). Among the two types, type 1 DM is mostly prevalent in Northern European countries whereas type 2 is mostly found in Africa and Asian countries like Sri Lanka (Gunathilaka et al., 2020). According to the most recent World Health Organization (WHO), statistics, in 2017, 424.9 million were suffering from diabetes and it is predicted that this number will increase to 628.6 million people by 2045 (Standl et al., 2019).

Currently, glucose-lowering drugs are mainly used to control hyperglycemia in type 2 DM whereas patients with DM type 1 mainly rely on external insulin (Kooti et al., 2016). However, most of the available hypoglycemic drugs exhibit side effects causing serious medical problems such as severely compromised renal function, decompensated heart failure and liver diseases (Tran et al., 2020). Due to awareness among people about the side effects of those drugs, many people are now turning to natural medications. Compared to hypoglycemic drugs, natural medications are more compatible with the human body and exhibit lesser side effects. Further, research has proved that phytoconstituents present in natural extracts demonstrate effective and safe results in treating DM (Tran et al., 2020).

Pumpkin is a popular vegetable cultivated all over the world. It belongs to the genus *Cucubita* and the family *Cucurbitaceae*, which is among the most extensive plant families in the plant kingdom. While there are numerous types cultivated globally, only a limited selection of varieties can be found in Sri Lanka. Currently, the seeds, leaves, and flesh of pumpkins have received considerable attention due to their nutritional value and health benefits.

Pumpkin seeds are an abundant reservoir of biologically active compounds including carotenoids, provitamins, tocopherols, phenolic compounds and their derivatives, phytosterols, triterpenoids, unsaturated fatty acids, flavonoids, protein, magnesium, potassium and phosphorus and possess effects which are biologically beneficial for humans, including anti-cancer and anti-diabetic properties (Dotto & Chacha, 2020). Additionally, previous studies have confirmed that pumpkin leaves (*Telfaria occidentalis*, family- *Cucurbitaceae*) also contain high levels of fats, protein, oils, minerals and vitamins (Mohd et al., 2016).

However, the bioactive compounds present in plants vary depending on environmental conditions. The production of bioactive compounds is influenced by the climate and geographical locations in which it manifests (Méndez-Flores et al., 2021). Moreover, a study emphasizes that the composition of carotenoids vary in different types of pumpkins (Bergantin et al., 2018). Hence, biological activities depend on the composition of bioactive compounds which vary with climatic conditions and the type of pumpkin.

Only limited research studies have been conducted worldwide to determine the hypoglycemic effects of pumpkin seeds, and pumpkin leaves. In a study (Li et al., 2016) using pumpkin seed oil, it was found that the hypoglycemic effect was due to the inhibition of alpha-amylase and alpha-glucosidase, which will be discussed in detail later. Also, Abd-elnoor (2019), using both pumpkin seed powder and oil, pumpkin seeds were shown to significantly lower blood glucose in alloxan-induced diabetic rats. Investigations employing aqueous (Chukwudi et al., 2018) and methanol extracts (Abubakar et al., 2021) of pumpkin leaves revealed substantial blood glucose decrease in similar rat models. Further, some studies have been conducted regarding the bioactive compounds present in pumpkin seeds and leaves and how they stimulate different mechanisms to reduce blood glucose levels. Pumpkin seeds contain bioactive compounds like quercetin, rutin, Vitamin E, and β -carotene, which contribute to their ability to lower blood sugar levels (Thakur & Bhasin, 2023). These compounds have various effects that support this potential, such as quercetin's role in reducing hypertension and vasoconstriction associated with diabetes, rutin's promotion of glucose uptake, Vitamin A's benefits improving glucose tolerance, and Vitamin E's enhancement of insulin secretion and reduction of oxidative stress (Thakur & Bhasin, 2023). On the other hand, pumpkin leaves contain a variety of bioactive compounds, including phenols, alkaloids, tannins, glycosides, steroids, and flavonoids (Abubakar et al., 2021). Among these compounds, phenols and alkaloids stand out for their hypoglycemic effects. While most studies have mainly examined the hypoglycemic effects of pumpkin seeds and leaves individually, this article focuses on investigating the combined potential of both pumpkin seeds and leaves to reduce hyperglycemia.

Therapeutic targets of hyperglycemia

Generally, the primary objective of type 2 diabetes management is to decrease elevated blood glucose levels. Gunathilaka et al (2020) argue that one way to achieve this is by targeting the reduction of postprandial hyperglycemia. They find that this can be accomplished by hindering the activity of enzymes responsible for breaking down carbohydrates, specifically α amylase and α glucosidase, which play crucial roles in carbohydrate metabolism. α - amylase assists in the digestion

of complex carbohydrates, breaking them down into smaller molecules. Similarly, α glucosidase aids in the breakdown of starch and disaccharides, converting them into glucose. Therefore, α -amylase and α -glucosidase function as crucial digestive enzymes and promote the absorption process within the intestines, and the inhibitors of these enzymes can be targeted to reduce postprandial hyperglycemia. Inhibitors of α -amylase function as blockers of starch, capable of binding to the active site of the amylase enzyme and modifying its catalytic function. As a result, they effectively lower the level of glucose in the bloodstream. On the other hand, α -glucosidase inhibitors work by diminishing the speed at which glucose is absorbed in the intestines (Gunathilaka et al., 2020). They achieve this by competitively and reversibly inhibiting the breakdown of disaccharides and oligosaccharides (Li et al., 2016). Therefore, natural substances which inhibit α -amylase and α -glucosidase can act as an effective treatment for hyperglycemia in diabetes.

Besides using enzymes that break down carbohydrates, inhibiting certain enzymes like angiotensin-converting enzymes and dipeptidyl peptidase-4 can also be used as a treatment strategy for type 2 DM (Gunathilaka et al., 2020). The enzyme known as angiotensin-converting enzyme participates in the renin-angiotensin-aldosterone system by converting angiotensin I into angiotensin II. Angiotensin II is a powerful constrictor of blood vessels and promotes the release of aldosterone by the adrenal cortex, which increases the absorption of sodium and water. This activation of the renin-angiotensin-aldosterone system results in higher blood pressure, leading to microvascular and macrovascular complications in individuals with type 2 diabetes mellitus. Consequently, inhibitors of angiotensin-converting enzyme have the capacity to reduce blood pressure, thereby helping to mitigate the long-term complications associated with diabetes (Thakur et al., 2021).

Similarly, Gunathilaka et al (2020) and Deacon (2019) find that dipeptidyl peptidase-4 (DPP-IV) plays a role in glucose metabolism and works to lower the levels of incretin hormones, such as glucose-like peptide-1 (GLP-1). GLP-1 is a hormone produced in the gut that helps to reduce blood sugar levels by promoting insulin secretion during hyperglycemic states in individuals with type 2 diabetes. However, once the patient's blood glucose levels return to normal, the effect of GLP-1 on insulin secretion gradually decreases. As a result, inhibitors of dipeptidyl peptidase-4 can increase GLP-1 levels, which in turn stimulates insulin secretion and helps to maintain hyperglycemia in patients with type 2 DM (Deacon, 2019; Gunathilaka et al., 2020).

Bioactive compounds present in pumpkin seeds and leaves

Fundamental facts about pumpkin seeds

There are two types of pumpkin seeds: hulled or husked seeds and hull-less or naked seeds. The hulled seeds appear as yellow-white husks while hull-less seeds appear as very thin dark green skin as shown in Figure 1. Both seeds are rich in bioactive compounds (Ayyildiz et al., 2019).



Figure 1: Hulled (a) and hull-less (b) seeds of *Cucurbita pepo* (Source: Loy & Murkovic, 2010)

Pumpkin seeds have been increasingly recognized in recent years for their bioactive components which possess significant nutraceutical and therapeutic benefits (Rezig et al., 2019). Furthermore, they can promote many beneficial health effects in humans including the reduction of blood glucose level and cholesterol levels, improvement of immune reactions and liver, prostate, and bladder health, and anti-inflammatory, anti-depression, and anti-cancer activities (Syed, 2019). While pumpkin cultivars exist worldwide in diverse forms, the commercially significant types are primarily *Cucurbita pepo* (the most prevalent), *Cucurbita moschata*, *Cucurbita maxima*, *Cucurbita mixta* and *Cucurbita stilbo*.

In addition, pumpkin seeds are a byproduct of the pumpkin fruit and are inexpensive but have priceless nutritional value. These can be easily obtained as by-products from industrial and domestic wastes such as oil extraction (Gao et al., 2022).

Bioactive compounds of pumpkin seeds

Pumpkin seeds are high in polysaccharides, vitamin E (tocopherols), unsaturated fatty acids, carotenoids, provitamins, proteins, pyrazine, pigments, phytosterols, squalene, saponins, triterpenoids, flavonoids, phenolic compounds

and their derivatives and coumarins (Loy & Murkovic, 2010). Moreover, pumpkin seeds provide a beneficial supply of essential nutrients like potassium, magnesium, phosphorus, and various trace minerals including iron, sodium, zinc, manganese, calcium, and copper (Amin et al., 2019). Certain bioactive minerals among these can function together at different or similar locations within the body, offering the potential to enhance bodily functions, support overall health, and decrease the likelihood of non-communicable ailments such as tumors, diabetes, high blood sugar, and complications associated with oxidative stress (Dotto& Chacha, 2020). The nutritional compounds of the pumpkin seeds are summarized in Table 1.

Table 1: Nutritive value of pumpkin seeds (per 100 g) by different studies (Amin et al., 2019; Rezig et al., 2019)

Nutrient (mg)	Nutritional value (Dry basis)	Nutritional value (Wet basis)
Energy	311.54	-
Ash	3.54	3.47
Moisture	56.74	6.96
Protein	21.31	40.00
Carbohydrate	5.18	-
Total sugars	9.73	1.15
Total fiber	46.65	12.89
Fat	23.45	35.53
Ascorbic acid	15.00	-
Iron	6.02	7.07
Sodium	1.35	189.81
Calcium	4.00	44.92
Potassium	434.71	471.70
Zinc	18.78	8.42
Copper	0.31	89.84
Phosphorus	0.74	1471.24
Magnesium	4.35	527.85
Manganese	1.35	3.93

Multiple research investigations (Amin et al., 2019; Siano et al., 2016) indicate that the dominant fatty acids present in pumpkin seed oil (PSO) comprise oleic, linoleic, stearic, and palmitic acids, which collectively constitute over 95% of

the total fatty acids. Among these, approximately 75% are categorized as unsaturated fatty acids (UFAs). Further lower concentrations of linolenic and arachidic acid have been reported (Benalia et al., 2019; Dotto & Chacha, 2020; Meru et al., 2018). Linoleic and alpha-linolenic acids are vital fatty acids for humans, and they cannot be produced within the human body. Therefore, they need to be obtained from dietary sources. Extensive research (Amin et al., 2019; Meru et al., 2018) has been conducted on unsaturated fatty acids due to their significant role in safeguarding against cardiovascular ailments. Additionally, these fats play a crucial part in promoting proper development and minimizing the likelihood of various forms of cancer, coronary heart disease, high blood pressure, and arthritis (Dotto & Chacha, 2020; Gažová et al., 2019).

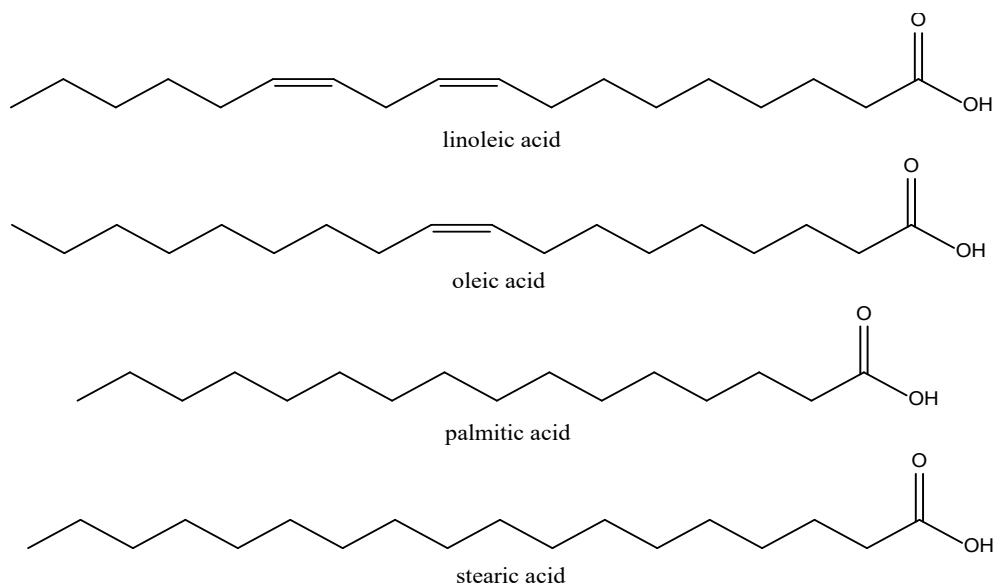


Figure 2: Structures of fatty acids present in pumpkin seed oil

Pumpkin seeds have a high vitamin E reserve and they contain four tocopherols (α , β , γ , and δ) and tocotrienol isomers (Azzi, 2019). Tocopherols and tocotrienols, which are strong antioxidants, have isomers that vary based on the location and quantity of the methyl group in the chromanol ring. These compounds can effectively neutralize potent radicals by freeing H^+ ions from their rings. By doing so, they protect cells from lipid peroxidation, thus reducing the risk of oxidative threats (Azzi, 2019; Bharti et al., 2013; Traber et al., 2021). The tocopherol levels found in pumpkin seed oil varied between 27 mg/g and 75 mg/g for α -tocopherol, 75 mg/g and 493 mg/g for γ -tocopherol, and 35 mg/g and 1110 mg/g for δ -tocopherol, according to recorded data (Bharti et al., 2013).

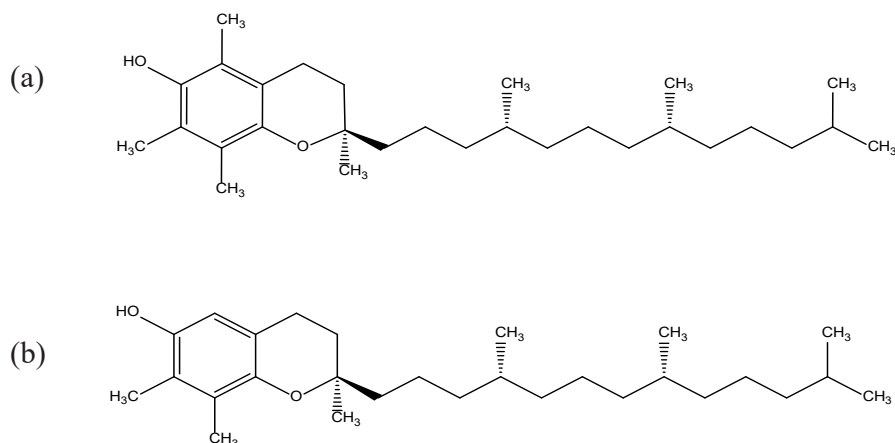


Figure 3: Structures of alpha (a) and gamma (b) tocopherols

Moreover, the study of pumpkin seeds confirm that they are a good source of carotenoids mainly β -carotene (Hussain et al., 2021). Carotenoids are lipid-soluble natural pigments and the most widely distributed carotenoids among *Cucurbita* spp. are α - and β -carotene, lycopene, lutein, zeaxanthin, and β -cryptoxanthin (Ninčević Grassino et al., 2023).

Bioactive compounds of pumpkin leaves

The main transpiration process of most plants occurs in their leaves, which are also a rich source of protein, minerals, and sugar due to the process of photosynthesis. Pumpkin leaves are particularly nutrient-dense, containing high levels of protein, fat, and vitamins, which have important nutritional, medicinal, and industrial applications. Extracts from pumpkin leaves can increase iron levels in the blood and support the structure of biological membranes through the presence of glycerolipids. The major fatty acid found in leaves, α -linolenic acid, has been shown to be involved in photosynthetic electron transport (Kaur et al., 2020).

Since few studies have been conducted on pumpkin leaves, this article focuses on *Telfaria occidentalis* leaves, which is one species that has been studied extensively (abd-elnoor, 2019; Abubakar et al., 2021).

Telfaria occidentalis is a plant species commonly known as the “fluted pumpkin” or “ugu” in Nigeria. It belongs to the family *Cucurbitaceae* (Aguebor-Ogie et al., 2021; Mohd et al., 2016). There are several significant findings in the latest research conducted by Mohd et al. (2016). *T. occidentalis* leaves possess a significant proportion of protein (56%) and carbohydrate (26.82%), whereas the fat content (2%) is comparatively minimal. Moreover, these leaves contain saponin, alkaloids, and tannins, with the aqueous extract having a significantly higher amount

of these compounds. The mineral analysis of *T. occidentalis* reveals the presence of significant quantities of Na, Mg, Ca, K, Cu, and Zn. Sodium plays a vital role in regulating plasma volume, maintaining acid-base balance, and facilitating nerve and muscle function. Magnesium, an essential component of chlorophyll, is important and helpful to manage ischemic heart disease and calcium metabolism in bones. Iron is a crucial component of hemoglobin. The leaves of *T. occidentalis* contain a substantial amount of calcium, which promotes the growth and maintenance of bones, teeth, and muscles. Zinc plays a crucial role in supporting the normal function of the immune system and acts as a component of more than 50 enzymes in the body. As a result, *T. occidentalis* leaves can fulfill the daily requirements of Na, Ca, Mg, and Zn (Enujiugha, 2014; Mohd et al., 2016).

In vitro and in vivo hypoglycemic potential of pumpkin seeds and leaves

In vitro hypoglycemic potential

Currently, studies have been conducted on various pumpkin species for their hypoglycemic potential.

The extract from *C. maxima* seeds at different concentrations (ranging from 6.2 to 500 mg/mL) was found to significantly suppress the function of α -amylase and α -glucosidase ($P < 0.05$) (Jane Monica et al., 2022). Pumpkin seeds exhibited significant inhibitory effects on α -amylase and α -glucosidase activities, with an 85% inhibition of α -amylase at a concentration of 500 mg/mL and a 91.16% inhibition of α -glucosidase at the same concentration (Jane Monica et al., 2022). IC_{50} values for α -amylase and α -glucosidase inhibition assay were estimated as 138 and 22 mg/mL, respectively. After examining the IC_{50} values, it can be inferred that pumpkin seeds demonstrated greater inhibition of α -glucosidase compared to the inhibition of α -amylase. (Jane Monica et al., 2022). A study conducted by Monica et al. (2020) proved the ability of pumpkin seed protein to inhibit the action of α -amylase significantly in a dose-dependent manner ($p < 0.05$).

A research study demonstrated that the *C. pepo* seed oil obtained by the Cavitation-accelerated aqueous enzymatic extraction (CAEE) method had a slightly higher inhibitory activity against α -amylase compared to the Soxhlet extraction (SE) method (Li et al., 2016). The IC_{50} value (a measure of inhibition) for CAEE seed oil was lower ($40.68 \pm 1.22 \mu\text{g/mL}$) indicating greater inhibition activity towards α -amylase compared to SE ($45.46 \pm 1.29 \mu\text{g/mL}$) and the standard acarbose ($53.35 \pm 1.60 \mu\text{g/mL}$). However, the *C. pepo* seed oil did not exhibit any significant inhibitory activity against α -glucosidase ($IC_{50} > 1000 \mu\text{g/mL}$) compared to the standard acarbose (IC_{50} : $37.96 \pm 1.14 \mu\text{g/mLs}$) (Li et al., 2016).

An in vitro study confirmed that *T. occidentalis* (fluted pumpkin) demonstrated a dose-dependent inhibition of α -amylase activity (0-0.2 mg/mL) (Obboh et al., 2012).

The extract of *C. pepo* leaves exhibited a promising ability to inhibit α -amylase, with an IC_{50} value of $24.99 \pm 0.07 \mu\text{g/mL}$, when compared to acarbose, the standard drug, which had an IC_{50} value of $19.45 \pm 0.19 \mu\text{g/mL}$. Further, *C. pepo* leaves extract showed α -glucosidase inhibitory potential exhibiting IC_{50} : $22.29 \pm 0.27 \mu\text{g/mL}$, whereas acarbose showed an IC_{50} equal to $16.70 \pm 0.09 \mu\text{g/mL}$ (Chigurupati et al., 2021).

Liang et al. (2021) confirm the antioxidant and ACE inhibitory activities of protein hydrolysate extracted from pumpkin seeds. According to the study, globulin mainly 11S globulin, and albumin mainly 2S albumin present in protein hydrolysate exhibited potent inhibitory activity on ACE. This proved that pumpkin seed proteins are a potential source of diverse bioactive peptides which inhibit the activity of ACE (Liang et al., 2021).

A study conducted using *T. occidentalis* revealed that the potency of ACE-inhibitory activity was significantly increased ($p < 0.05$) after the fluted pumpkin leaf isolate (FLI) underwent enzymatic hydrolysis using chymotrypsin and alcalase enzymes (Famuwagun et al., 2020). Results showed that both hydrolysates (chymotrypsin and alcalase hydrolysates) exhibited lower IC_{50} values (0.666 and 0.675 mg/mL , respectively), indicating a greater inhibitory potency compared to standard proteins pepsin (1.432 mg/mL) and trypsin (0.889 mg/mL). This proved the strong inhibitory potential due to the presence of a greater number of peptide molecules in the hydrolysates. Further, the active site of the enzyme might have stronger interactions with smaller peptides compared to the larger protein molecules present in FLI. When analyzing the composition, both hydrolysates contained higher levels of aromatic amino acids (AAA), branched-chain amino acids (BCAA), histidine-containing amino acids (HAA), and sulfur-containing amino acids (SCAA). Therefore, the study attributes protein hydrolysates with strong ACE-inhibitory activities to the high concentration of hydrophobic amino acids (Famuwagun et al., 2020).

Jane Monica et al. (2022) also find that ethanol extract obtained from *C. maxima* seeds showed inhibition of DPP-IV enzymes at different concentrations (ranging from 6.2 to 500 mg/mL) ($p < 0.05$) and that at 500 mg/mL concentration, the pumpkin seeds were able to effectively inhibit 81.20% of DPP-IV action. The IC_{50} values were estimated to be 246 mg/mL for the DPP-IV inhibition assay. Comparing the IC_{50} values suggest that pumpkin seeds are a more effective inhibitor of DPP-IV activities (Jane Monica et al., 2022).

In vivo hypoglycemic potential

Hussain et al. (2022) prove that pumpkin seeds led to a reduction in blood sugar levels in alloxan-induced diabetic rats. *C. maxima* seeds have a hypoglycemic impact in streptozotocin-induced diabetic rats (Sharma et al., 2013).

In vivo studies confirm that pumpkin seeds decreased blood glucose levels in alloxan-induced diabetic rats. Hussain et al. (2022) examine the hypoglycemic impact of pumpkin seed powder in comparison to pumpkin peel and flesh powder. This discovered that pumpkin seed powder exhibited a significant hypoglycemic effect in rats with diabetes induced by alloxan, unlike pumpkin peel and flesh powder.

Sharma et al. (2013) confirm the hypoglycaemic effect of *C. maxima* seeds in streptozotocin-induced diabetic rats. The group of rats with untreated diabetes demonstrated a continuous rise in their blood glucose levels throughout the entire study, whereas the rats that received treatment with *C. maxima* seeds experienced a noteworthy decrease in blood glucose levels. This reduction was particularly significant in streptozotocin-induced diabetic rats compared to the control group (Sharma et al., 2013).



Figure 4: Fruits, seeds, and leaves of the studied pumpkin species

Sources: Olubusoye et al., 2021; Otto & Verloove, 2020

Conclusion

From above analysis and discussion, it is evident that pumpkin seeds and leaves are a reservoir of highly bioactive compounds which exhibit many valuable health-promoting properties. This article mainly discusses the bioactive compounds present in pumpkin seeds and leaves and how they activate different antidiabetic mechanisms. Many studies have identified the hypoglycemic potential of pumpkin seeds and leaves mainly via the inhibitory activity of α -glucosidase, α -amylase, ACE, and DPP-IV enzymes. Most of these studies have confirmed the antidiabetic potential of pumpkin seeds and leaves. However, it is necessary to conduct further research to determine the many different mechanisms which induce hypoglycemic effects of pumpkin seeds and leaves. Additional research is also required to isolate the active compounds which can lead to drug development. Further, it is crucial to increase public awareness of the hypoglycemic potential of pumpkin seeds and leaves to enhance consumption to reduce diabetic cases.

Conflict of interest

The authors declare that they have no conflict of interest.

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