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Pumpkin seeds: Nutritional profile, bioactives and effect in type 2 diabetes

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Abstract
Type 2 diabetes has emerged as a significant global health concern, prompting a growing demand for accessible and sustainable alternative treatments. The potential therapeutic role of bioactive compounds derived from various natural sources has been extensively studied in treatment of diabetes. However, these compounds demonstrate a multitude of biological activities. Their diverse mechanisms of action contribute to their ability to effectively manage diabetes. Pumpkin seeds have garnered attention due to their abundant bioactive compounds, such as antioxidants, polyphenols, and phytosterols. Thus, extensive researches have showcased the positive impact of these compounds on regulating blood glucose levels, enhancing insulin sensitivity, and reducing oxidative stress in individuals with type 2 diabetes. This review paper focuses on the effect of bioactive compounds found in pumpkin seeds on type 2 diabetes and emphasizes the need for exploring the potential therapeutic approach. The findings from this review underscore the potential of incorporating pumpkin seeds into the diet as a natural and cost-effective approach to managing type 2 diabetes, thereby opening up exciting avenues for future research and treatment strategies.

Keywords: Pumpkin seeds, Type 2 diabetes, bioactive compounds, hypoglycemic properties, blood glucose level

Introduction

The World Health Organization defines health as a comprehensive and holistic state of well-being, which encompasses physical, mental, and social dimensions. These dimensions collectively contribute to overall sense of well-being in individual (Tiwari and Talreja 2020) [60]. The prevalence of diabetes and obesity has significantly risen globally. However, diabetes is a global health crisis and a pandemic, endangering both human well-being and global economies. Thus, the immediate action is imperative to address this pressing issue and mitigate its impact on individuals and societies worldwide (Zimmet *et al*., 2014) [62]. As per the forecast shared by The International Diabetes Federation, diabetic cases are expected to exceed 783 million globally by 2044 whereas the count is already surpassing the 415 million as recorded in 2015. Alarmingly, it is estimated that half of diabetes patients remain undiagnosed because of less developed health care system which increasing their susceptibility to developing complications associated with the disease (Papatheodorou *et al*., 2018: Sherrell, 2022) [44, 53].

Diabetes is a condition arises when body becomes unable to maintain blood glucose level because of decrease secretion, unavailability, or functional incapability of insulin hormone (Nall, 2021) [40]. However, diabetes manifests in three primary forms Type 1 diabetes, Type 2 diabetes, and Gestational diabetes. IDDM (Insulin dependent diabetes mellitus) or type 1 diabetes characterised by reduced or no production of insulin hormone in body (Anonymous, 2023) [4]. The condition occurs due to destructed β cells as a result of autoimmune process (Janež *et al*., 2020) [30]. On the other hand, NIDDM (Non-insulin dependent diabetes mellitus) is considered as the most common type of metabolic disorder at global level. Under such condition, loss in cellular insulin sensitivity, insulin resistance and alteration in metabolic status of body takes place at the prior manner (Gupta *et al*., 2016) [24]. While, the gestational diabetes is a condition occurs during the pregnancy period in women without pre-existing diabetes. Whereas, due to the hormonal changes and weight gain during pregnancy further leads to diminish the effectiveness of insulin and develops insulin resistance. Similarly, the pancreas also cannot produce adequate insulin to overcome this resistance and also contribute for the development of gestational diabetes (Zambon, 2020) [61]. Although, diabetes (Chronic metabolic disorder), can lead to a wide range of complications affecting various organs and systems in the body. These are cardiovascular and coronary diseases, kidney damage and other nephropathy, eye damage, nerve damage etc. This condition also become the root cause to develop musculoskeletal complications, oral complications, respiratory complications, mental health complications, acute complications and can further lead to death (Ndjaboue *et al*., 2020) [42].

However, lifelong insulin replacement therapy is essential to start at first from diagnosis in individuals with Type 1 Diabetes Mellitus (T1DM). While, various treatment options, such as human insulin and insulin analogues, are currently accessible for managing T1DM (Silver *et al*., 2018) [54]. Similarly, a range of oral pharmacological agents are currently available for the treatment of Type 2 Diabetes Mellitus (T2DM). These includes ten classes such as sulfonylureas, meglitinides, metformin (A biguanide), thiazolidinediones (TZDs), alpha glucosidase inhibitors, dipeptidyl peptidase IV (DPP-4) inhibitors, bile acid sequestrants, dopamine agonists, sodium-glucose transport protein 2 (SGLT2) inhibitors, and oral glucagon-like peptide 1 (GLP-1) receptor agonists etc. (Chaudhury *et al*., 2017) [12]. Additionally, injectable options include GLP-1 receptor agonists, dual GLP-1 receptor and GIP receptor agonists, and amylin are also available (Feingold, 2022) [20].

On the other side, the treatments available for diabetes are associated with certain drawbacks including the development of drug resistance. The condition further causes reduced drug effectiveness, potential side effects, followed by risk of toxicity in some cases (Chaudhury *et al*., 2017) [12]. For instance, some studies shown the reduced effectiveness of sulfonylureas in patients after six years of treatment. Moreover, it has been noted that glucose-lowering drugs may not effectively control the condition of hyperlipidemia. Additionally, healthcare professionals need to carefully consider the side effects of medications and their *in vitro* interactions with each other (Kooti *et al*., 2016) [32]. While, natural products and their active compounds are promising alternatives for treating type 2 diabetes and its complications, without adverse effects. However, extensive researches have demonstrated the therapeutic potential of various medicinal plants and effectiveness of their bioactive molecules to combat diabetes (Gothai *et al*., 2016) [23].

Plants serve as valuable natural sources of bioactive compounds and are commonly utilized as functional food ingredients. Among these, pumpkin seeds are particularly noteworthy due to their abundance of functional components. Therefore, this review highlights the utilization of pumpkin seeds in the context of type 2 diabetes mellitus (T2DM), emphasizing their high content of bioactive compounds.

Pumpkin as a potential source

Pumpkin is a large, round fruit from the *Cucurbita*ceae family, which also includes cucumber, melon, and squash. The fruit originated in North America and has been cultivated for thousands of years (Chomicki *et al*., 2020) [13]. The *Cucurbita*ceae family comprises around 130 genre and 800 species, including various plants such as squash, pumpkin, melon, and gourds. While, the plant is grown primarily in warm climate, and its fruit, flowers, and seeds are commonly consumed in the form of food (Ozuna and León-Galván, 2017) [43]. The *Cucurbita* genus includes mainly three cultivated species named as *Cucurbita pepo L., C. moschata,* and *C. maxima* (Hernandez *et al*., 2023) [26]. However, pumpkin is a valuable source of phytochemicals, with high concentration found in its pulp, peel, and seeds. These parts contain abundant polyphenols and flavonoids, known for their powerful antioxidant properties (Hashash *et al*., 2017) [25]. Furthermore, pumpkin pulp is rich in vitamins, antioxidants such as carotenoids, lutein, zeaxanthins, as well as a variety of essential minerals, making it highly suitable for human consumption (Adubofuor *et al*., 2018) [1].

Nutritional profile of pumpkin seeds

Despite being considered as agro-industrial waste, pumpkin seeds are nutrient-rich and possess nutraceutical properties (Pham *et al*., 2017) [46]. Pumpkin is a disease-preventing vegetable with a global annual production of 27 million metric tons (Pocketbook, 2015) [47]. In pumpkin seeds, the approximate composition includes 25.19% carbohydrates, 25.4% protein, 41.59% oil, and 5.34% fiber. Moreover, these seeds are abundant in bioactive compounds like gallic acid, total sterols, and tocopherols (Gohari *et al*., 2011; Syed *et al*., 2019) [22, 58]. Pumpkin seeds are notable for their protein content, essential fatty acids (Omega-3 and omega-6), and dietary fiber (Rani *et al*., 2021) [50]. The pumpkin pulp and seed powder are a plentiful source of essential minerals like zinc, phytochemicals, and beta-carotene, providing an abundance of these valuable nutrients and offers numerous health benefits (Boujemaa *et al*., 2020: Hussain *et al*., 2021) [10, 29].

Bioactive compounds in pumpkin seeds

Pumpkin seeds are actually a store of various nutrients that possess fascinating nutraceutical properties (Amin *et al*., 2019) [2]. These seeds are rich in a diverse array of bioactive compounds including tocopherols, squalene, carotenoids, provitamins, pigments, pyrazine, saponins, phytosterols, triterpenoids, coumarins, unsaturated fatty acids, flavonoids, and phenolic compounds. Although, the phenolic compounds found in pumpkin seeds encompass tyrosol, vanillin, p-hydroxybenzoic acid, caffeic acid, ferulic acid, and vanillic acid. In addition, seeds contain trace amounts of luteolin, protocatechuic acid, trans-p-coumaric acid, and syringic acid (de la Rosa, 2019; Dotto and Chacha, 2020; Singh and Kumar, 2023) [16, 18, 56]. Pumpkin seed protein comprises of cucurbitin, a compound that includes salt-soluble globulin, prolamins, glutelins, and albumins. The presence of phytosterols like campesterol, β-sitosterol, and stigmasterol are also notably present in pumpkin seeds. These constituents contribute to the diverse protein profile and provide health-promoting phytosterols in pumpkin seeds because of their bioactive activity (Singh and Kumar, 2022) [55].

Pharmacological properties of pumpkin seeds

Plants have been used for food and medicine for centuries. Pumpkin has gained recognition in traditional medicine for its therapeutic properties. Utilising bioactive substances from natural sources is one of the possible treatments for a number of medical disorders (Rahman *et al*., 2022) [48]. Specific characteristics of these substances may help explain why they have therapeutic benefits. Pumpkin includes a number of bioactive chemicals that have the potential to provide certain health advantages (Samtiya *et al*., 2021) [51].

Flavonoids and triterpenoids present in pumpkin seeds contribute to their potential anticancer action mechanism (Chari *et al*., 2018) [18]. Phytoestrogen compounds such as secoisolariciresinol and lariciresinol found in pumpkin seeds have estrogen-like effects. These effects contribute to the prevention of hyperlipidemia and osteoporosis in menopausal women (Lestari and Meiyanto, 2018) [35]. Pumpkin seeds, rich in polyunsaturated fatty acids, help reduce the risk of atherosclerosis. They also contain ribosome-inactivating proteins with antiviral and antifungal effects. Pumpkin seeds have shown effectiveness in anxiety treatment, attributed to their content of tryptophan (Lindseth *et al*., 2015: Shaban and Sahu, 2017) [37, 52].

The anti-inflammatory effects of pumpkin seeds can be attributed to the presence of beta-carotene and phenolic compounds (Ramak and Mahboubi, 2019) [49]. The phenolic compounds found in pumpkin seeds contribute to their beneficial antioxidant activity (Nawirska- Olszańska *et al*., 2013) [41]. Including pumpkin seeds in your diet can reduce serum triglyceride levels. It can also decrease lipid accumulation in hepatocytes and increase cholesterol excretion in feces. While, these effects demonstrate the hypotriglyceridemic potential of pumpkin seeds (de Farias *et al*., 2022) [15]. The antioxidant properties of pumpkin seeds are associated with their anticarcinogenic effect. Pumpkin seeds possess bioactive compounds that exhibit antioxidant properties, contributing to their potential in preventing or inhibiting the development of cancer (Batool *et al*., 2022) [6]. The presence of tryptophan and hydroxytryptophan, an intermediate metabolite in the synthesis of serotonin, is linked to the antidepressant effect of pumpkin seeds. These components play a role in influencing neurotransmitter levels and potentially modulating mood, suggesting the potential use of pumpkin seeds as a natural approach to support mental well-being. (Dotto and Chacha, 2020) [18].

As per some studies, consuming more pumpkin extract has demonstrated positive effects on glycemic control, lipid profile, and pancreatic β cell health. These benefits are linked to the presence of bioactive compounds like flavonoids, triterpenoids, steroids, and polyphenolic components. The wide range of bioactive compounds in pumpkin extract may contribute to its potential in improving metabolic outcomes and supporting pancreatic function. (Bayat *et al*., 2014; Marbun, *et al*., 2018) [7, 39]. Cucurmoschin, derived from pumpkin seed protein, inhibits the growth of fungi like *Botrytis cinerea*, *Fusarium oxysporum*, *Mycosphaerella arachidicola*, and *Mycosphaerella oxysporum*. The antifungal effect of cucurmoschin is likely due to its translation-inhibiting activity. These findings indicate that cucurmoschin, as an antifungal protein, has the potential to hinder mycelial growth in different fungal species, making it a promising natural antifungal agent. (Suresh and Sisodia, 2018) [57].

Bioactive compounds responsible for anti-diabetic effect of pumpkin seeds

Pumpkin is widely utilized as an anti-diabetic agent in numerous countries. The hypoglycemic activity of pumpkin is linked to the presence of gelatin (Amin and Thakur, 2013) [3]. Pumpkin seeds contain compounds such as quercetin, genistein, rutin, Vitamin E, and β-carotene, which have been associated with their hypoglycemic effects. These bioactive constituents contribute to the potential blood sugar-lowering properties of pumpkin seeds (Lestari and Meiyanto, 2018; Azzi, 2019; Cuco *et al*., 2019; Peng *et al*., 2021; Dhurve *et al*., 2022;) [35, 5, 14, 45, 17] Bioactive compounds exhibit diverse effects on type 2 diabetes, both in *in vivo* and *in vitro* settings. For instance, in *in vivo* conditions, Quercetin aids in reducing hypertension and vasoconstriction induced by diabetes (Mahmoud *et al*., 2013) [38]. While, within *in vitro* conditions, quercetin enhances glucose uptake, facilitates GLUT4 translocation, and reduces hepatic glucose production (Eid *et al*., 2015) [19]. In terms of β-cell proliferation, genistein promotes an increase. Moreover, within the *in vivo* experiments, genistein demonstrates its efficacy by reducing hyperglycemia induced by STZ (Streptozotocin), as well as elevating blood insulin levels, improving glucose tolerance, and regulating β-cell proliferation and apoptosis (Fu *et al*., 2010) [21].

Rutin exhibits enhanced glucoe uptake in *in vitro* conditions (Kappel *et al*., 2013) [31] and demonstrates the ability to decrease blood glucose levels in *in vivo* experiments (Hsu *et al*., 2014) [28]. However, vitamin A has been observed to elevate insulin mRNA levels and stimulate insulin secretion in *in vitro* conditions. Additionally, *in vivo* conditions shows that vitamin A has potency to reduce adipose lipid stores, enhance muscle mitochondrial content, improve glucose tolerance, and mitigate insulin resistance (Li *et al*., 2019) [36]. On the other hand, vitamin E enhances insulin secretion, reduces oxidative stress, and decreases apoptosis *in vitro* (Lee *et al*., 2012) [34] and *in vivo*. Whereas, it decreases alloxan-induced hyperglycemia, increases insulin secretion, alleviates oxidative stress, and reduces pancreatic apoptosis (Takemoto *et al*., 2016) [59]. D-chiro-inositol (D-CI), a natural bioactive compound found in the *Cucurbitaceae* family, acts as an insulin mediator. However, D-CI has demonstrated significant anti-hyperglycemic properties, effectively controlling blood glucose levels in individuals with Type-2 diabetes (Hosen *et al*., 2021) [27].

In a 2017 study by Kushawaha *et al*., observed that the pumpkin seed extract was effectively showing the hypoglycemic and anti-diabetic effects. The researchers attributed these effects to the stimulation of insulin release from pancreatic β-cells. This suggests that pumpkin seed extract holds promise as a potential therapeutic agent for managing blood sugar levels and diabetes. Pumpkin seeds showed hypoglycemic effects in rats with PX-407-induced diabetes. While, the pharmacological evidence supported the potential of pumpkin seeds as a hypoglycemic agent. Multiple botanical components interacted to target different aspects of diabetes. Tocopherols were identified as key contributors. Whereas, the findings emphasize the significant role of bioactive compounds, particularly tocopherols, in pumpkin seeds for managing diabetes (Bharti *et al*. in 2013) []9.

Pumpkin seeds are abundant in pectin, a dietary fiber known for its ability to regulate blood glycemic levels. When diabetic patients consume fiber-rich foods like pumpkin seeds, it can help reduce the reliance on insulin. This suggests that incorporating pumpkin seeds into the diet of individuals with diabetes may offer benefits in glycemic control due to the presence of pectin (Bharti *et al*., 2018) [8].

Conclusion

In conclusion, numerous scientific studies have focused on investigating the potential therapeutic advantages of pumpkin, including its ability to mitigate muscular dystrophy, diabetes, hypertension, cancer, and inflammatory disorders. The bioactive compounds found in pumpkin seeds have demonstrated promising effects on type 2 diabetes. Numerous studies have highlighted their potential in regulating blood sugar levels, improving insulin sensitivity, and reducing oxidative stress in diabetic individuals. These findings indicate that incorporating pumpkin seeds into the diet may offer a natural and accessible approach to managing type 2 diabetes. In addition, the exploration of potential synergies between pumpkin seeds and other natural compounds or medications holds promise for maximizing their therapeutic efficacy in managing type 2 diabetes. Although, bioactive compounds can enhance diabetes management but should not replace prescribed medications or lifestyle modifications. Additionally, researches are required to ascertain optimal dosages, long-term effects, and individual variability in response. Overall, the exploration of pumpkin seed bioactive compounds holds great promise for advancing our understanding and treatment of this prevalent metabolic disorder.

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