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Pumpkin Seed Intervention to Control Diabetes Mellitus: A Systematic Review

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Abstract

BACKGROUND: In overcoming the problem of diabetes, developed countries have used herbal plants as an alternative treatment, considering that various types of synthetic drugs and available insulin therapy have physiological consequences in their use, such as insulin resistance, anorexia nervosa, brain atrophy, and fatty liver.

AIM: This article aims to identify pumpkin seed interventions in controlling diabetes mellitus.

METHODS: The article review was conducted using three bibliographic databases. Articles were selected based on 2011–2021 publications using the PRISMA flowchart of 2015.

RESULTS: A total of 1405 were obtained from three databases. About 17 articles according to the inclusion criteria and seven articles were selected in this literature review. Based on the literature review results, it was found that the previous researchers combined pumpkin seed with other plants to assess its efficacy in controlling blood glucose. Pumpkin seed had been tested on many experimental animals such as mice, rats, and rabbits. It showed hypoglycemic activity.

CONCLUSION: Pumpkin seed is an herbal plant that has advantages in preventing and maintaining health as well as being used as a complementary therapy for people with diabetes mellitus.

Introduction

Diabetes is an epidemic disease that can cause complications and slowly attack other important organs in the body, resulting in premature death and disability. High blood glucose causes an increased risk of death from diabetes and other cardiovascular disease risks [1]. Diabetes is one of the four non-communicable diseases that are a priority for world leaders. Developed countries no longer dominate the disease of diabetes; even in the past three decades, the prevalence of diabetes has increased more rapidly in low- and middle-income countries. Diabetes reduces life expectancy by 5–10 years, which in 2030 is predicted to be the seventh leading cause of death in the world [2]. One in 11 adults in the world has diabetes. Ninety to ninety-five percent of diabetes cases are type 2 diabetes, and one in two people living with diabetes are unaware they have diabetes [3].

In overcoming the problem of diabetes, developed countries have used herbal plants as an alternative treatment, considering that various types of synthetic drugs and available insulin therapy have physiological consequences in their use, such as insulin resistance, anorexia nervosa, brain atrophy, and fatty liver [4]. One of the herbal plants that have been widely used as a complement to the treatment of diabetes mellitus is pumpkin or known by the scientific name Cucurbita/pumpkin. In Western countries, pumpkin has become an herbal preparation and food plant that replaces synthetic medicine and insulin therapy in preventing and treating diabetes mellitus; it has attracted worldwide attention. Natural phenolic compounds of pumpkins are potential antioxidants and bioactivity as medicine [5]. This compound can be found in stems, leaves, flowers, and fruits. In human body, flavonoid functions as an antioxidant, protection of cell structures, and increasing the anti-inflammatory activity of Vitamin C and antibiotics. The consumption of antioxidants for instance carotenoids, polyphenols, and tocopherols can prevent oxidative stress. China has used more than 200 species of plants, including pumpkin and many other common plants, as an alternative treatment and prevention of diabetes mellitus. Likewise, other countries, such as Yugoslavia, Argentina, India, Brazil, and America, have also traditionally used pumpkins to treat diabetes mellitus [6]. This article aims to identify pumpkin seed interventions in controlling diabetes mellitus.

Methods

This review article was compiled systematically using PRISMA 2015 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines).

Articles were selected based on the publications of the past 10 years, namely, 2011–2021, through three computerized bibliographic databases, including ScienceDirect, PubMed, and Google Scholar, using the keywords of intervention, pumpkin seeds, and diabetes mellitus through the Boolean operators "AND" and "OR." All selected references were imported into Mendeley. The inclusion criteria were: (a) Diabetes mellitus, (b) English articles, (c) peer-reviewed articles, and (d) pumpkin seed intervention.

All articles imported to Mendeley were selected for duplication; selected articles would be further selected by reading the title and abstract, and inappropriate articles would be deleted. Relevant articles would be further selected based on inclusion criteria, and the selection was conducted by reading the entire contents of the article. Selected articles were then entered into the synthesis table.

Quality assessment was carried out using the Strengthening the reporting of observational studies in Epidemiology (STROBE) checklist [7]. The guide consists of 22 items grouped into eight quality assessment criteria: Sample size, sampling methodology, response rate, outcome measure, control analysis, study boundaries, ethical considerations, and controls for confounding scores assigned to each study range, which was reviewed from 0 to 8 points (0 if no criteria were met and 8 points if all criteria were met).

Results

Literature finding

Figure 1 show that a total of 1405 were obtained from three databases. About 17 articles according to the inclusion criteria and seven articles were selected in this literature review (Table 1). Based on the literature review results, it was found that the previous researchers combined pumpkin seed with other plants to assess its efficacy in controlling blood glucose. Pumpkin seed had been tested on many experimental animals such as mice, rats, and rabbits. It showed hypoglycemic activity.

Discussion

Pumpkin seeds are a good source of polyunsaturated fatty acids and antioxidants [14]. Pumpkin seeds contain vegetable oil, potassium, magnesium, calcium, and other sources of nutrients that are beneficial for health [15]. Pumpkin seeds also contain squalene (583–747 mg/100 g), a triterpene as a precursor to steroid hormones, cholesterol, and Vitamin D. Furthermore, it contains abundant sterols, such as stigmastatrienol and sterol spinasterol, with total concentrations of each ranged from 18.8 and 35.1 g/100 g and 18.2 and 23.3 g/100 g sterols [16].

The vegetable oil produced by pumpkin seeds has aroused interest since of the many studies linking its consumption with health benefits in several conditions such as atherosclerosis [17], prostate hypertrophy [18], urinary tract dysfunction [19], and other health benefits. Pumpkin seeds affect antioxidant, hypoglycemic, and hypolipidemic activities [20], [21]. This effect is attributed to the bioactive compounds present in pumpkin seed oil, such as carotenoids and tocopherols [21], [22]. According to the United States Department of Agriculture National Nutrient Database ([23], 100 g of organic pumpkin seeds contain 127 calories, 15 g carbohydrates (0 g sugar and 17.9 g fiber), 5 mg protein, 21.43 g fat (3.57 g is saturated fat), 20 mg calcium, and 0.9 g iron.

Pumpkin seeds are also a great source of magnesium, zinc, copper, and selenium. Pumpkin seeds also contain antioxidants and adequate polyunsaturated fatty acids, potassium, Vitamin B2 (riboflavin), and folate. Pumpkin seeds and seed oil also contain many other nutrients and plant compounds that have been shown to provide health benefits. The main fatty acids in pumpkin seed oil (PSO) are linoleic, oleic, stearic, and palmitic, which account for more than 95% of the total fatty acids, and about 75% of them are unsaturated fatty acids (UFA) [24], [25], [26], [27]. In addition to fatty acids, pumpkin seeds are also rich in protein which is nothing but a combination of amino acids contained in pumpkin seeds [28]. Amino acids play an important role as the building blocks of protein and as intermediates in metabolism. The supply of food with sufficient quantity and quality of essential amino acids is equally important for physiological functions in the human body [29].

According to the Office of Dietary Supplements [30], pumpkin seeds are also a good source of magnesium. Magnesium is one of the seven essential macrominerals. Magnesium is an important mineral that plays many roles in the body, including regulating blood pressure and blood sugar levels, relaxing blood vessels, and colon function [31], [32]. Magnesium deficiency in the older population is associated with insulin resistance [33], metabolic syndrome [34], coronary heart disease [35], and osteoporosis [36].

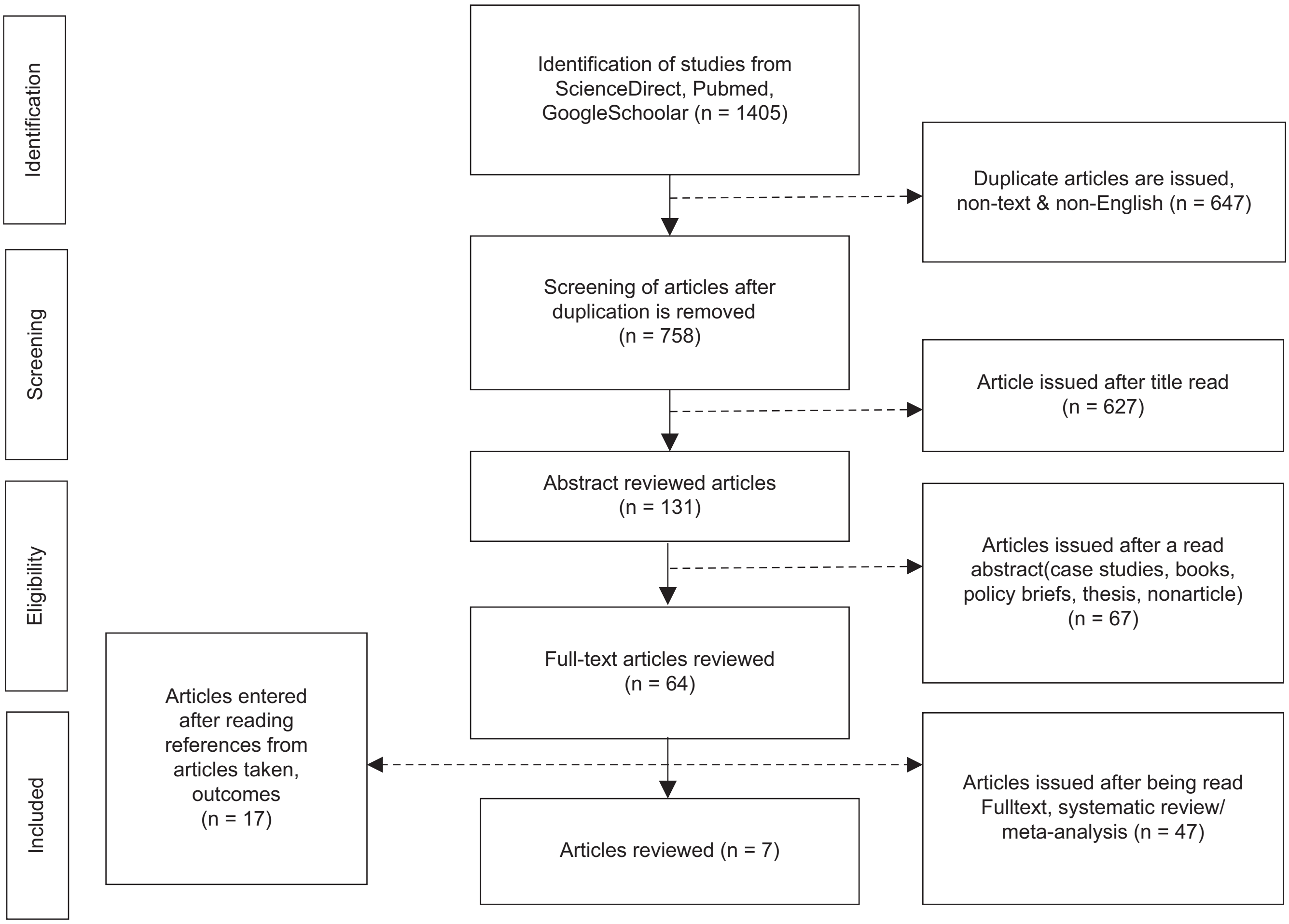

Figure 1: Flow chart for study based on PRISMA 2015 guidelines

Zinc in pumpkin seeds is required for various aspects of cellular homeostasis. It is involved in the catalytic activity of approximately 300 enzymes and plays a role in immune function, cell division, protein and deoxyribonucleic acid (DNA) synthesis and apoptosis. The human body has no specialized zinc storage system and so humans rely on a daily intake of dietary zinc to maintain health and prevent disease. It is well established that zinc has an insulin-like effect on all insulin sensitive tissues. Insulin exerts its effect by binding the insulin receptor and activating an intracellular signaling cascade mediated by the phosphoinositide 3'-kinase (PI3K/phosphoinositide 3-kinase)/Akt complex. Zinc (II) ions have been shown to activate this same complex in numerous human cell types. Zinc (II) ions have also been shown to suppress protein tyrosine phosphatases associated with the insulin signaling cascade thus activating the insulin signaling cascade resulting in glucose uptake, increased glycogen synthesis, and decreased gluconeogenesis [37].

Pumkin seed also contains biologically active ingredients such as polysaccharides, Dietary polysaccharides enhance pancreatic β-cell mass, trigger insulin signaling pathways through insulin receptors, and activate the PI3K/Akt pathway (phosphoinositide 3-kinase/serine/threonine-specific protein kinase). They modulate extracellular-signal-regulated kinase (ERK)/c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinase (MAPK) pathways and, thus, alleviate β-cell dysfunction. Polysaccharides have been documented to have potent anti-diabetic activity. β-d-(1→6)-glucan can improve the insulin level and hepatic glycogen accumulation, decreasing the blood glucose level in streptozotocin (STZ)-induced diabetic mice [38].

Zhu *et al.* (2015) demonstrated a low molecular weight and well-characterized polysaccharide from pumpkin fruit that prevented β-cell apoptosis by regulating the messenger RNA (mRNA) expression of Bcl-2 and Bax in STZ-induced damage of pancreatic islet cells. They found that polysaccharides from pumpkin possessed strong antioxidant capacities and eventually decreased the nitric oxide level and restore the β-cells [39]. Zhang *et al.* (2017) also presented that water-soluble polysaccharide purified from pumpkin restored the damaged pancreatic islets via triggering β-cell multiplication [40]. This investigation further observed that intragastric treatment of polysaccharide from pumpkin significantly decreased blood glucose, total cholesterol, triglycerides, and HbA1c (glycated hemoglobin) in alloxan-induced diabetic animals and restored the normalization within 21 days' treatment of polysaccharides [41].

Table 1: Summary of selected studies

Intervention	Author, Year, Country	Subject	Result
Gymnadenia orchidis (Orchid) root salep and pumpkin seed	Arzoo *et al*. (2018) [8], India	Adult female albino mice (n=30, bodyweight 45–50 g) strain BALB C	The results showed that the combination of *Gymnadenia orchidis* (Orchid) root Salep (with pumpkin seed *(Cucurbita maxima*) was significantly able to normalize changes in biochemical parameters of different diabetic rats. DNA damage in the blood cells of diabetic mice could be reversed with this supplementation. Terpenoids from the root of the ointment and antioxidants from pumpkin seeds played an active role in fighting diabetes. The fibrous root of Gymnadenia orchidis was collected from the local market in Darjeeling, West Bengal, and India. The root Salep was prepared by suspending the powder root in double distilled water and used at an effective dose (200 mg/kg body weight) to the diabetic animals through oral supplementation
Soy germ extract-pumpkin seed extract	Shim *et al*., (2014) [9], South Korea	120 women aged between 35 and 70 years, suffering from urinary urgency, frequent urination, and nocturia, with or without incontinence for more than 3 months	The results showed that after 12 weeks. The intervention group was given Cucuflone (a combination of soy germ extract-pumpkin seed extract) experienced a significant decrease compared to the control group. The decrease occurred in: 1. Frequency of urination 2. Urgency 3. Frequency of incontinence 4. Maximum urgency score 5. Frequency of nocturnal urination and 6. Overactive bladder (OAB) symptom scale While the placebo group showed significant differences in: 1. Frequency of urination 2. Frequency of incontinence 3. Overactive bladder (OAB) symptom scale
Pumpkin (*Cucurbita maxima*) Fruit and Seeds Powders	Gabal, (2019) [10], Egypt	About 60 adult albino rats of the Sprague-Dawley strain (200±5 grams) were grouped into five groups of ten each.	The results showed that pumpkin extract caused a significant increase in blood glucose, insulin levels, and glycated hemoglobin percentage compared to the control group. Pumpkin seed extract also increased antioxidant activity and healed the islets of Langerhans by increasing their number and size compared to the control group
Pumpkin Seeds Powder and Oil	Gabal, (2019) [10], Egypt	About 60 adult male albino rats of Sprague-Dawley strain weighing between (200±10 g)	The results showed that pumpkin seeds are rich in carbohydrates, protein, crude fiber, and crude oil and contain many unsaturated fatty acids, especially linoleic acid and oleic acid. It is a high source of antioxidants. This intervention also proved that pumpkin seed extract and oil were not only able to reduce glucose, glycated hemoglobin, cholesterol, triglycerides, LDL (low-density lipoprotein), VLDL (very low-density lipoprotein), and lipid peroxidation significantly but also able to increase HDL (high-density lipoprotein-cholesterol and insulin) in diabetic rats compared to the control group
Flax and pumpkin seed mixture powder	Makni *et al*., (2011) [11], Tunis	Male Wistar Rat (11–12 weeks old, weighing 190–210 g)	The study indicated that Flax and pumpkin seed mixture powder (a combination of ax and pumpkin seeds) added to food potentially prevented diabetes complications in adult rats
Seeds of *Cucurbita pepo*	Bharti *et al*., (2013) [12], India	Healthy male albino Wistar rat (150–160 g)	The results provided pharmacological evidence of seeds of *Cucurbita pepo* as anti-hyperglycemic agents mediated by interactions of various plants with multiple targets operating in diabetes mellitus
Cucurbitaceae seeds	Teugwa *et al*., (2013) [13], Cameroon	3-months-old male albino Wistar rat weighing 285–310 g	The results showed that the selected Cucurbitaceae seeds contained globulins with significant anti-hyperglycemic activity. Therefore, it is highly recommended to investigate the development of peptide and/or phytomedicine drugs from this bioactive protein that can be used as an affordable alternative therapy against diabetes mellitus

Pumpkin can reduce blood glucose levels allegedly because it has flavonoids, saponins, terpenoids, beta-carotene, Vitamin A, and Vitamin E [5]. Flavonoids are antioxidants that can reduce insulin resistance, increase insulin sensitivity, and improve the function of beta cells. The results of another study showed that administration of pumpkin water extract with a dose range of 56–112 mg/200 gBW/day for 14 days was able to reduce fasting blood glucose levels in diabetic rats [42]. The mechanism of anti-diabetic pumpkin is derived from the activities of protein-bound polysaccharides which have been proven to reduce blood glucose concentrations, increase blood levels of serum insulin and improve tolerance to glucose in the alloxan- induced rat which destroys cell β and therefore, induce diabetes [43].

Conclusion

Pumpkin seed is an herbal that has advantages in preventing and maintaining health as well as being used as a complementary therapy for people with diabetes mellitus. The primary efficacy of pumpkin seeds has also been tested on experimental animals. Pumpkin seeds have also been shown to contain many nutrients that affect hypoglycemic activity.

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