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A Review on Hypoglycemic Effects of the Urtica dioica L. and Punica granatum L. Plants

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ABSTRACT: Diabetes mellitus is a disease characterized by insulin resistance, impaired insulin secretion, or increased blood sugar resulting from the development of both. This disease has four forms depending on type 1, type 2, gestational diabetes and special causes. Type 2 diabetes results in the loss of body cells' ability to respond to insulin, starting with high blood sugar. This disease is important due to its widespread occurrence in the world, high treatment costs and no exact treatment yet. In this review, knowledge will be given about the hypoglycemic effects of Stinging Nettle (*Urtica dioica* L.) and Pomegranate (*Punica granatum* L.) plants grown in our country.

Key Words: Pomegranate, stinging nettle, hypoglycemic effect

1 INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Diabetes; It is divided into four groups as type 1, type 2, gestational diabetes mellitus (gestational diabetes mellitus) and diabetes due to specific causes [2]. Type 1 diabetes is an autoimmune disease that occurs when T-cells in the immune system attack the body's own insulin-producing cells, called beta cells, in the pancreas. Type 2 diabetes, is the result of the inability of body cells, which initially started hyperglycemia, to not fully respond to insulin, a condition defined as 'insulin resistance' [3].

Diabetes mellitus is an endocrine disease with symptoms such as polyuria, polyphagia and polydipsia [4]. This disease causes life-threatening acute complications such as hyperosmolar nonketonic coma, diabetic ketoacidosis and hypoglycemic coma, and chronic complications such as heart diseases, hypertension, vascular diseases, stroke, retinopathy, nephropathy and neuropathy [5].

Approximately 537 million of the world's adults who are between the ages of 20-79 have diabetes. The total number of individuals in this age group represents 10.5% of the world population. This total is expected to rise to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045. Approximately 240

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million people worldwide are living with undiagnosed diabetes. This means that almost one in two adults has diabetes but they are unaware of their condition. Almost 90% of people who are with undiagnosed diabetes live in low- and middle-income countries. In Southeast Asia and the Western Pacific and Africa, more than half of people with diabetes are undiagnosed. More than 1.2 million children and adolescents have type 1 diabetes. More than half (54%) of these are under 15 years of age. According to a systematic review of the literature, the incidence of diabetes was stable or declining in more than 70% of mostly high-income populations from 2006 to 2017. More than 80% of countries have reported a decline or stability in diabetes incidence since 2010 [3]. The widespread prevalence of diabetes and the high cost of treatment, nonetheless coupled with the lack of a definitive cure, make it an attractive research topic [5].

Various medicinal plants are used against diabetes in the world and in our country. In this review, information about the morphology, biochemical content, medicinal purposes and uses of stinging nettle and pomegranate plants used against diabetes are also given.

2 Medicinal Plants with Hypoglycemic Effect

2.1 Stinging Nettle (Urtica dioica L.)

Figure 1. Stinging Nettle (*Urtica dioica* L.) [6]

Stinging nettle (*Urtica dioica* L.) is in the Nettle family [7]. It is a dioecious, perennial and herbaceous plant. It is usually less than one meter tall. It is widespread in Turkey and has been distributed everywhere in terms of growing area. The leaves of this herb are opposite and the edges are toothed. Its flowers are quite small, female or male flowers are collected in a mixed manner and form clusters on the stem [8,9].

2.1.1 Biochemical Content of the Plant

Stinging Nettle leaves, which are rich in minerals, contain plenty of peel, zinc, phosphorus, magnesium, potassium, rubidium, bromine, potassium, chlorine, nitrogen, chromium, molybdenum, nitrogen, manganese, iron, cobalt, copper, boron, calcium and aluminum. In addition, there are vitamins such as riboflavin, thiamine, niacin, A, C and K, as well as cellulose, carbohydrate and betaine groups. Its seeds contain palmitic

acid, linoleic acid, glycerol, oleic acid and various proteins. All of the stinging nettle contains acetophenone, acetic acid, ferulic acid, acetylcholine, P-coumaric acid, folacin, coproporphyrin, histamine, lycopene, protoporphyrin, butyric acid, serotonin and xanthophyll [10,11].

2.1.2 Medicinal Use of Stinging Nettle

The leaves, stem, seeds and roots of stinging nettle are used for therapeutic purposes [12]. It is used in kidney disorders, preventing hair loss, asthma, high blood pressure, goiter, stopping bleeding, respiratory tract disorders, as an expectorant, some fungal infections, eczema, rheumatoid arthritis, abdominal pain, It is used in hemorrhoids, cancer treatment, diabetes, and it is also known to increase urine, purify blood, stimulate appetite, relieve skin damage, regulate digestion, prevent bone resorption, stop diarrhea and start milk secretion. It is used for various purposes in the world. In Turkey it is used for eczema, rheumatism, diuretic, bronchitis, blood diseases, blood sugar lowering, headaches, urinary tract diseases, blood production, as a stimulant, asthma, gall bladder, spleen and liver diseases; in Brazil for gout, diarrhea, prostate, diuretic, diabetes, allergy; in Canada for alopecia, chest diseases, childbirth, rheumatic diseases, pain, irritation; Rheumatism, prostate, diuretic in Germany; gout, sprains, rheumatism, irritation reliever in India; cancer, mental illness, epilepsy, nervous breakdown, diuretic, rheumatism, back pain, prostate, high blood pressure in the USA; eczema, asthma, ulcer rheumatism, intestinal inflammation, diabetes, muscle and joint pain in Peru [13,14].

2.1.3 Use of Stinging Nettle in Diabetes

Aqueous extract obtained from stinging nettle leaves caused a decrease in blood serum glucose level and an increase in serum insulin level 30 min after I.P. administration to diabetic rats. It is suggested that the lowering effect of this extract on blood glucose level is due to increased insulin secretion from the chambers of Langerhans [15]. Aqueous extract of stinging nettle given to rats by gastric gavage at a dose of 500 mg/kg did not cause any change in blood glucose level. On the contrary, when given at a dose of 250 mg/kg, a strong antihyperglycemic effect was observed in the first 1 hour after glucose administration to rats under oral glucose tolerance test. It has been suggested that this observed effect may be a result of the absorption of glucose from the intestine [16]. It was stated that when hydroalcohol extract of stinging nettle leaves was given to rats at a dose of 100 mg/kg by I.P. route, the decrease observed in blood glucose was similar to the control group [17,18]. It was observed that administration of the ethanolic extract of stinging nettle root to rats at a dose

of 150 mg/kg via I.P. had a corrective effect on the recovery of high blood sugar and ovarian disorders [19]. When the hydroalcohol extract of stinging nettle was given to rats at a dose of 100 mg/kg i.p., it caused a significant decrease in blood sugar [20]. Aqueous-alcoholic extract of stinging nettle has been proven to have a statistically significant lowering effect on blood glucose level at the end of 21 days after it was given to diabetic rats at a dose of 200 mg/kg by I.P. route [21]. In a study by Dowlatkhah et al., administration of stinging nettle extract to diabetic rats at a dose of 200 mg/kg caused a significant lowering effect on blood glucose levels. Furthermore, there was a significant increase in insulin level [22]. Based on these studies, it can be concluded that the use of stinging nettle in diabetic individuals will have significant beneficial effects on blood glucose and insulin levels.

2.2 Pomegranate (*Punica granatum* L.)

Figure 2. Pomegranete (*Punica granatum* L.) [23]

Punica granatum L. is a plant species belonging to the Punicaceae (Hookah) family. This plant grows in the provinces around the Mediterranean and in subtropical areas of countries such as India, Pakistan and China. They are trees in the form of small unbranched or thorny bushes that can reach 2-7 meters in height. The leaves have different shapes from lanceolate to obovate, 2.5-7 cm, their edges are smooth and hairless. The flowers are red and rarely white. Hypanthium is red in color and leathery. Sepals articulated at the base and about 8 mm. Petals are 15-20 mm. The fruit is round, 5-8 cm in diameter and brownish in color. Its seeds are embedded in the fruit. It blooms in May and June. It grows in bushes and limestone slopes at an altitude of 250-600 m [24-26]. It is widely grown in Western, Northern, Southeastern Anatolia and the Islands in Turkey [24].

2.2.1 Biochemical Content of Pomegranate

As a result of the researches on this plant, different substances have been detected in fruit peels, flowers, fruit juices, leaves, seeds and shells in terms of biochemical content. The flowers of this plant contain diglycoside, urolic acid, daucosterol, D-mannitol, ursolic acid, asiatic acid, pelargonidin 3,5, brevifolincarboxylate, pomegranatate, maslinic acid, sitosterol, ellagic acid and gallic acid. In fruit juice contain citric acid, invert sugar, thiamine, vitamins B1 and B2, vitamin

C, riboflavin, various amino acids (methionine and valine), flavonols (quercetin, rutin), anthocyanins (cyanidin, delphinidin, pelargonidin), flavan-3 -ols (catechin, epigallocatechin). Besides, malic, fumaric, tartaric, ascorbic, succinic, ellagic, chlorogenic, caffeic, p-coumaric and quinic acids are also present. Finally, in the fruit peel, there are phenyl propanoids (caffeic acid, chlorogenic, quinic, p-coumaric acid), flavan-3-ols (catechin, epicatecin, epigallocatecin-3-O-gallate), tannins (casuarin, corylagin, pedunculagin, gallajildilactone, gallic acid, tellimagrandin, garnet B, garnet A, ellagic acid), flavones (luteolin 7-O-glycoside, luteolin), flavonols (chemferol, quercetin, kemferol 3-O-glycoside, rutin, chemferol 3-O-ramnoglycoside), anthocyanins (cyanidin, delphinidin, pelargonidin), alkaloids (pelletierin), flavanone (naringin) [26].

2.2.2 Medicinal Use of Pomegranate

Traditionally, pomegranate juice-dried peels have been used orally as an antispasmodic, antihysteric, astringent, diuretic, carminative, and emanagogue. In India, the juice of green fruits, cloves, ginger, and thuja are mixed with honey and the juice of ripe fruits is used against colds with saffron. In China, the peels of this fruit are traditionally used in the treatment of burns. In addition, the peels are also used in allergic dermatitis, acne and infections [27-29].

2.2.3 Use of Pomegranate in Diabetes

The hypoglycemic effect of pomegranate is due to its seeds, flowers and fruit juice. Furthermore, ursolic, gallic and oleanolic acid compounds have antidiabetic effects [30]. Aqueous extract of pomegranate peels administered adlubitum to rats caused protection of pancreatic tissue and subsequent stimulation of insulin release, regeneration and increase in pancreatic beta cells. It also caused stimulation by activation of insulin receptors [31]. Administration of ethanolic extracts of pomegranate flowers (200 and 400 mg/kg doses) to rats caused a decrease in blood glucose and an increase in liver glycogen and plasma insulin levels. 400 mg/kg dose of ethanolic extract showed a stimulatory effect on insulin [32]. It was observed that the hydroalcoholic extract of pomegranate peel caused a significant decrease in blood glucose level when administered to rats at a dose of 200 mg/kg i.p. and 600 mg/kg orally. In addition, it has been observed that pomegranate peel administered orally at a dose of 600 mg/kg has a significant regulatory effect on insulin [33]. It was observed that pomegranate peel (250 mg/kg) and pomegranate juice (5 ml/kg) extracts given to rats via I.P. significantly decreased blood glucose and caused an increase in insulin level compared to the

diabetic group. They also caused a decrease in alpha-amylase level [34]. The methanolic extract obtained from pomegranate leaves was given orally to rats at doses of 100, 200 and 400 mg/kg for 8 weeks. As 100 mg/kg dose decreased blood glucose level at the end of the 8th week, 200 and 400 mg/kg doses caused a decrease in blood glucose at the end of the 6th week [35]. Aqueous-ethanol (50%) extract of pomegranate given orally to diabetic hyperglycemic rats caused a lowering effect on blood glucose [36]. Hydro-methanolic extract of pomegranate peel administered to diabetic rats via gastric gavage at a dose of 200 mg/kg resulted in a statistically significant decrease in blood glucose and HbA1C levels compared to the control group [37]. Administration of methanolic extract obtained from the leaves of pomegranate plant to diabetic rats at a dose of 400 and 600 mg/kg by gastric gavage method provided a statistically significant decrease in blood glucose level, while a significant increase in insulin level [38].

3 CONCLUSION

Complementary medicine applications using herbal preparations are widely used all over the world for the prevention and treatment of various health problems, especially diabetes [39,40]. In this review, it was tried to give information about nettle and pomegranate plant, which are widespread in the world and in our country, and to shed light on new studies.

4 AUTHOR CONTRIBUTIONS

Hypotesis: Y.Y.; Design: Y.Y.; Literature review: Y.Y.; Data Collection: Y.Y.; Manuscript writing: Y.Y.

5 CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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