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Pomegranate and type 2 diabetes

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ABSTRACT

Over the last decade, various studies have linked pomegranate (*Punica granatum* Linn), a fruit native to the Middle East, with type 2 diabetes prevention and treatment. This review focuses on current laboratory and clinical research related to the effects of pomegranate fractions (peels, flowers, and seeds) and some of their active components on biochemical and metabolic variables associated with the pathologic markers of type 2 diabetes. This review systematically presents findings from cell culture and animal studies as well as clinical human research. One key mechanism by which pomegranate fractions affect the type 2 diabetic condition is by reducing oxidative stress and lipid peroxidation. This reduction may occur by directly neutralizing the generated reactive oxygen species, increasing certain antioxidant enzyme activities, inducing metal chelation activity, reducing resistin formation, and inhibiting or activating certain transcriptional factors, such as nuclear factor κB and peroxisome proliferator–activated receptor γ. Fasting blood glucose levels were decreased significantly by punicic acid, methanolic seed extract, and pomegranate peel extract. Known compounds in pomegranate, such as punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids, have been identified as having anti-diabetic actions. Furthermore, the juice sugar fraction was found to have unique anti-oxidant polyphenols (tannins and anthocyanins), which could be beneficial to control conditions in type 2 diabetes. These findings provide evidence for the anti-diabetic activity of pomegranate fruit; however, before pomegranate or any of its extracts can be medically recommended for the management of type 2 diabetes, controlled, clinical studies, are needed.

1. Introduction

Diabetes prevention and treatment are high priorities in medical research. Fruit extracts have been used extensively in this context because they are natural, safe, and readily available. Moreover, folk medicine suggests some possible benefits to their use. One such example of these fruits is pomegranate (*Punica granatum* Linn) (Family Punicaceae), a fruit native to the Middle East [1]. Different parts of this plant are used in indigenous Indian medicine to cure various diseases, particularly diabetes [2].

Pomegranate fractions from different parts of the fruit have been linked with the prevention and treatment of a wide range of disorders and diseases, including cardiovascular

Abbreviations: NF-κB, nuclear factor κB; ROS, reactive oxygen species; PFE, pomegranate flower extract; PPAR, peroxisome proliferator-activated receptor; LPO, lipid peroxidation; PON1, paraoxonase 1; TGs, triglycerides; ZDF rats, Zucker fatty diabetic rats; STZ rats, streptozotocin-induced diabetes rats; LDL, low density lipoprotein; HDL, high density lipoprotein; GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; PSO, pomegranate seed oil.

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disease, cancer, Alzheimer disease, erectile dysfunction, male infertility, arthritis, brain ischemia, dental diseases, obesity, and diabetes [3,4]. The therapeutic potential of pomegranate fractions is due to the presence of unique bioactive compounds with antioxidant, anti-inflammatory, anti-infective, anti-atherogenic, anti-carcinogenic, and anti-hyperglycemic effects [4-6].

The connection between pomegranate and diabetes was discussed by Katz et al, 2007 [7]. Katz and his group concluded that pomegranate extracts and their active compounds could be effective in the treatment and prevention of type 2 diabetes. Later reviews that addressed the therapeutic effects of pomegranate in general [3] or the cardioprotective benefits of pomegranate juice [8] have indirectly discussed the link between pomegranate and diabetes. More recently, a review by Medjakovic and Jungbauer (2013) focused on the potential use of pomegranate and its compounds in therapy for metabolic syndrome [4].

This review summarizes studies that have evaluated pomegranates, pomegranate extracts, and its components on diabetes and related factors associated with biochemical and metabolic conditions of diabetes. The review is organized by the type of investigation conducted such as cell cultures, animal models and human clinical trials. Also, presented herein are the potential mechanisms by which the extracts of pomegranate and some of their identified components affect the conditions associated with diabetes.

1.1. *Cell culture studies*

Table 1 summarizes the in vitro studies performed on pomegranate and derived compounds and their reported effects. Nuclear factor κB (nuclear factor κ light-chain enhancer of activated B cells; NF-κB) is a protein complex that is found in almost all animal cell types and controls DNA transcription. It is involved in cellular responses to stimuli, such as reactive oxygen species (ROS), cytokines, and various forms of radiation [9]. Pomegranate wine (2.0 μg/mL) was found to inhibit the activation of NF-κB in cultured vascular-endothelial cells [10,11]. Studies performed on human acute monocytic leukemia cell line-1-differentiated macrophages showed that the traditional anti-diabetic effect of the methanolic extract of pomegranate flowers (PFE) at 500 mg kg^{-1} d^{-1} is due to the enhancement of peroxisome proliferator-activated receptor (PPAR)-γ, a transcription factor that plays an important role in carbohydrate metabolism [12]. A study performed by Parmar and Kar (2008) noted that aqueous pomegranate peel extract at 2.0 μg/mL inhibited the H_2O_2-induced lipid peroxidation (LPO) in rat red blood cells [13]. A later study showed that 1.25 to 10 μmol/L punicic acid, a conjugated linolenic acid isomer found in pomegranate, increased PPAR-α and -γ reporter activity in 3T3-L1 pre-adipocytes [14]. Koren-Gluzer et al (2011) found that pomegranate juice and 50 μmol/L punicalagin, a major polyphenol in pomegranate, increased insulin release from a β-tumor cell line, an effect similar to the activity of the paraoxonase 1 (PON1) enzyme [15]. Very recently, it has been shown that the addition of pomegranate fruit extract, rich with ellagic acid, at 50–100 μg/mL to differentiated murine 3T3-L1 adipocytes reduced the secretion and intracellular levels of resistin, an adipocytokine, by promoting its degradation at the protein level [16].

2. Rodent studies

2.1. *Effects of pomegranate peels*

A study performed on Wistar albino male rats revealed that the administration of aqueous pomegranate peel extract (200 mg/kg) reduced the concentrations of glucose in serum and LPO in cardiac, hepatic, and renal tissues [13]. The treatment of alloxan-induced diabetic rats for 10 days with 200 mg/ pomegranate peel extract, rich in polyphenols, resulted in lower fasting serum glucose and higher insulin levels as well as anti-lipid peroxidation effects [17].

2.2. *Effects of pomegranate flowers*

Pomegranate flowers have been used in Unani and Ayurvedic folk medicines to cure diabetes [18]. In 2000, a study conducted by Jafri et al on normal and alloxan-induced diabetic rats reported hypoglycemic activity (lowering blood glucose) of the aqueous-ethanolic (50%, v/v) extract (400 mg/kg) of pomegranate flowers [19]. Later, it was found that long-term oral administration of PFE (500 mg/kg) decreased the content of cardiac triglycerides (TGs) as well as plasma TGs, total

Table 1 – Cell culture studies on pomegranate fractions or phytochemicals on biochemical and metabolic variables related to type 2 diabetes

Affecter	Concentration	Effect	Target	Type of cells	References
Pomegranate wine	2.0 μg/mL	-	NF-κB	Vascular-endothelial cells	[10,11]
Pomegranate flower extract	500 mg kg^{-1} d^{-1}	+	PPAR-γ	Human acute monocytic leukemia cell line-1-differentiated macrophage cells	[12]
Pomegranate peel extract	2.0 μg/mL	-	H2O2-induced Lipid peroxidation	Rat red blood cells	[13]
Punicic acid	1.25-10 μmol/L	+	PPAR-α and -γ reporter	3T3-L1 pre-adipocytes	[14]
Punicalagin	50 μmol/L	+	Insulin	β-tumor cell line	[15]
Pomegranate fruit extract; Ellagic acid	50-100 μg/mL	-	Resistin	Differentiated murine 3T3-L1 adipocytes	[16]

(–) inhibition; (+) stimulation.