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Review

The antidiabetic and antioxidant properties of some phenolic phytochemicals: A review study

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ABSTRACT

Background: One class of phytochemicals are phenols with (−OH) group bounded to aromatic hydrocarbon group. The aim of this study was to review the anti-diabetic and anti-oxidant properties of important phenols.
Methods: This is a review study with ethic number (95s108) from AJUMS. About 450 articles (original, review,etc) been screened; 40 of them in the range of (1992−2017) were used due to their correlation to the study purpose. 28 of them were indexed by "Web of science (ISI)", 24 of them indexed by pubmed and also 29 of them were indexed by scopus data center.
Findings: Phenols affect diabetes in different ways. CGA suppress hepatic gluconeogenesis through the inhibition of G6Pase and is also an insulin sensitizer that potentiates insulin action. Curcumin reduce insulin resistance so decrease AGE's products in diabetes mellitus. Hydroxytyrosol regulates the calcium channels which plays key role in insulin secretion. Resveratrol increase the stimulation of glucose uptake and insulin secretion. CGA has similar antioxidant activity as vitamin E and ellagic acid maybe is even more potent than vitamin E. curcumin inhibits lipid peroxidation and scavenge superoxide anion and hydroxyl radicals. The antioxidant activity of hydroxytyrosol protects pancreatic cells from damage and death. Treatment with resveratrol significantly decreases the level of glucosylated hemoglobin.
Conclusion: All these phytochemicals have potent antidiabetic and antioxidant effects in different ways beside their other effects like anti-inflammatory and anti-carcinogenic properties in ellagic acid, or like anti-angiogenic and apoptogenic activities in curcumin. So we suggest further studies in the field of diabetes and antioxidation.

1. Introduction

Diabetes is characterized by raised blood sugar levels due to the defects in insulin secretion or action. According to the latest survey in 219 countries, among people egad 20−79 years, 382 million people have diabetes mellitus and it is estimated that this number will reach 592 million in 2035. But studies showed Compounds isolated from plants are used for the prevention and treatment of some diseases such as diabetes [1]. There are many phytochemicals in fruits and herbs and each work differently [2]. Phytochemicals are non-nutritive herbal chemicals which have different properties. They provide much of the color and taste in fresh or processed fruits and vegetables. plants produces these chemicals for self protection, and recently researches have demonstrated that many of them can also protect human against diseases [3]. A long-term increase in glucose is one of the most important causes of diabetes secondary disorders, such as angiopathy, neuropathy, retinopathy, deficiency in the antioxidant defense system, and lipid profile disorders [4]. Phenols are large number of naturally occurring molecules known for their antioxidative properties. Their synthetic form is being used in foods for protecting against oxidative rancidity [5] there is a wide range of natural pheneols that have antitumor, hypoglycemic, and free radical scavenging as well as antioxidant properties [6] like Arctium. lappa [7], Morus Nigra [8,9], Vitex Agnus-Castus [10] Grape juice [11] and many other plants. according to Iqbal et al. investigations Morus Nigra extract prevent diseases through antioxidant activity and radical scavenging because of its high phenolic compounds levels [8,9]. Another study demonstrated that phenols in Grape juice (GJ) could increase

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plasma antioxidant capacity and has protective effects on the vascular system. Boqué et al. have suggested that phenolic extracts may be good for reducing body fat [11].

Studies point to a strong consistent relationship between oxidative stress-induced hyperglycemia and progression of diabetic complications in patients with Type 1 and also in those with Type 2 diabetes mellitus [12]. The electrone delocalization in the aromatic nucleus of phenols is the main cause of their antioxidative potency. In fact, when these compounds react with the free radicals formed during autoxidation, they generate a new radical which is stabilized by the resonance effect of the aromatic nucleus. The propagation phase consisting of radical chain reactions is, therefore, blocked, and the development of rancidity delayed. [5] in this study we reviewed the anti-diabetic and anti-oxidant mechanisms of five phenols including chlorogenic acid (CGA), ellagic acid, curcumin, hydroxytyrosol and resveratrol.

2. Search methods

This study is a systematic review with ethic number (95s108) from AJUMS "Ahvaz Jundishapur University of Medical Sciences". About 450 articles of all types (original, review,etc) were searched using the "Phenols", "antidiabetic", "antioxidant", "chlorogenic acid", "ellagic acid", "hydroxytyrosol", "curcumin" and "resveratrol" as keywords. All the articles has been screened and but only 40 of them in the range of (1992–2017) were used due to their correlation to the study purpose. 28 of them were indexed by "Web of science (ISI)", 24 of them indexed by pubmed and also 29 of them were indexed by scopus data center.

3. Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene), is a naturally occurring phytoalexin present in numerous plant species exerts beneficial effects in the organism and may be helpful in preventing and treating some metabolic diseases, including diabetes. [13] resveratrol is produced by the plant to defend itself against fungal and other attacks. Resveratrol has been reported to elicit many cellular responses including cell cycle arrest, differentiation, and apoptosis, and has anti-inflammatory, anti-leukemic, antiviral, and neuroprotective properties [14]. In general, the management of diabetes involves three main aspects: reduction of blood glucose, preservation of cells, and, in the case of type 2 diabetes, improvement in insulin action. Data from the literature indicate that the beneficial effects of resveratrol in relation to diabetes comprise all these aspects. Interestingly, in experiments on isolated cells, resveratrol was able to stimulate glucose uptake in the absence of insulin. The stimulation of glucose uptake induced by resveratrol seems to be due to increased action of glucose transporter in the plasma membrane. Studies on rats with experimentally induced diabetes demonstrated increased expression of the insulin-dependent glucose transporter, GLUT4, as a result of resveratrol ingestion, compared with diabetic animals not given resveratrol [15]. Resveratrol is also reported to act as an insulin-secretagogue in different β-cell insulinoma lines which might contribute to its glucose lowering effect [16]. It should be mentioned, however, that in some experiments on rats with streptozotocin-induced diabetes, resveratrol appeared to be ineffective and failed to decrease blood glucose [15]. Resveratrol can also function as an antioxidant and reduces the risk of developing coronary heart disease, likely through its modulation of lipid metabolism and prevention of the low density lipoprotein oxidation forcing the cycle of oxidative stress and damage. Oral treatment with resveratrol decrease the levels of glycosylated hemoglobin, suggesting that it may prevent oxidative damage caused by the glycation reaction in diabetic conditions. It is found in grapes, mulberries, peanuts, the roots of white helleboreand, the roots of Polygonum cuspidatum [14] (see Fig. 1).

4. Curcumin

Curcumin is the principal curcuminoid found in turmeric (Curcuma longa Linn.), a popular spice in Asian cuisine [18]. Curcumin is a kind of yellow color of polyphenols extractive from genus Curcuma plants Curcumin possesses a variety of pharmacological qualities including anti-inflammatory, antioxidant, anti-angiogenic and apoptogenic activities [19]. Several studies in recent years have shown that curcumin is a potent inhibitor of tumor initiation in vivo and possesses antiproliferative activities against tumor cells in vitro [20]. Curcumin also enhances intestinal lipase, sucrase and maltase activity, and increases the activity of pancreatic lipase, amylase, trypsin and chymotrypsin [21]. Among the numerous reported therapeutic effects of curcumin, one of them is hypoglycaemic action. In experimental diabetes mellitus, the mechanism(s) underlying this effect could involve activation of PPARγ, the site of action of the thiazolidinedione class of antidiabetic drugs. Whilst this latter action would suggest an extrapancreatic effect of curcumin on blood glucose levels, one study demonstrates that curcumin also exerts a direct stimulatory effect on pancreatic β-cell function [22]. Curcumin prevents galactose-induced cataract formation at very low doses. Curcumin also decreases advanced glycation end products induced complications in diabetes mellitus. Curcumin is also reported to have antibacterial, antiamoebic and antiHIV activities [21]. In addition, it could delay development of T2DM, improve β-cell functions, prevent β-cell death, and reduce insulin resistance in animals [18]. The antioxidant properties of this yellow pigment appear to be an essential component underlying its pleiotropic biological activities. In fact, curcumin has been reported to inhibit lipid peroxidation and to effectively scavenge superoxide anion and hydroxyl radicals. Curcumin, in fact, neutralizes active oxygen species including superoxide, hydroxyl radical and nitric oxide. In renal epithelial cells, curcumin has been reported to inhibit lipid peroxidation resulting in protection against the cytotoxic action of hydrogen peroxide. Curcumin is a potent inducer of HO-1 in vascular endothelial cells both in normoxic and hypoxic conditions, and that increasing hemeoxygenase activity is an important element in curcumin mediated cytoprotection against oxidative stress. Curcumin is a major active component of the food flavor turmeric. It is extracted from the powdered dry rhizome of *Curcuma longa Linn (Zingiberacee),* a perennial herb widely cultivated in tropical regions of Asia [20] (see Fig. 2).

5. Chlorogenic acid

Chlorogenic acid (CGA) is an ester formed from cinnamic acids and quinic acid and is also known as 5-*O*-caffeoylquinic acid (5-

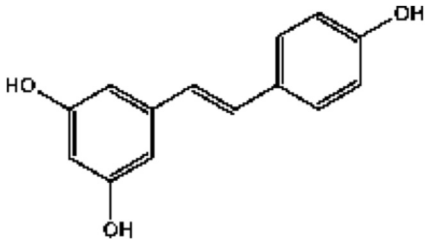

Fig. 1. Chemical structure of resveratrol [17].

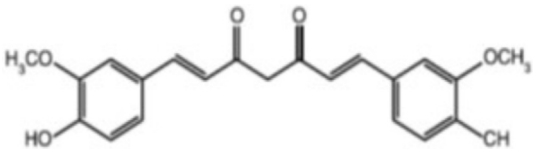

Fig. 2. Chemical structure of curcumin [23].

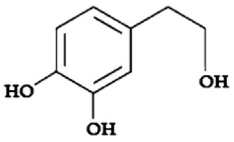

Fig. 4. Chemical structure of hydroxytyrosol [33].

CQA) (IUPAC numbering) or 3-CQA (pre-IUPAC numbering) [24]. CGA is a type of hydroxycinnamic acids, occurs in many types of fruits and in high concentration in coffee [25]. Many studies have suggested that polyphenols, especially Chlorogenic acid, have hypoglycemic effects [26]. CGA is a kind of insulin sensitizer that has similar performance to metformin in potentiating insulin action. CGA also suppresses postprandial hyperglycemia by inhibiting α-glucosidase like available α-glucosidase inhibitors such as acarbose, miglitol, and voglibose. In particular, CGA has been showed to have anti-hyperglycemic effects in humans [24]. CGA has been shown to inhibit glucose-6-phosphatase, the enzyme that catalyzes the final step of glycogenolysis and gluconeogenesis [26]. Chlorogenic acid has can delay glucose absorption in the intestine through inhibition of G-6-pase translocase and reduction of the sodium gradient driven apical glucose transport [24]. Besides, there are studies demonstrating that CGA stimulates glucose uptake in myotubes and adipocytes it has been shown that CGA stimulates glucose uptake in skeletal muscle through the activation of AMP-dependent kinase (AMPK) [25].

Chlorogenic acid exhibited higher DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging activity than vitamin E. In one study it has been shown that chlorogenic acid has similar antioxidant activity (EC50 17.8 μg/ml) to vitamin E (EC50 13.7 μg/ml) as a positive control. Moreover, preventive effects of CGA in the oxidation, lipid peroxidation and formation of hydroxyl free radical have been reported [26]. Chlorogenic acid also may favorably affect cardiovascular risk status by modestly reducing LDL oxidation susceptibility and decreasing LDL-cholesterol and malondialdehyde (MDA) levels [28]. In one study, the protective effect of chlorogenic acid on blood granulocytes from oxidative stress was also observed [29]. CGA can be found in Yacon leaves, plums, apples and cherries [26,29] (see Fig. 3).

6. Hydroxytyrosol

Among phenols, Hydroxytyrosol (3, 4-dihydroxyphenylethanol) stands out as a compound of high added-value, due to its interesting antioxidant and potential beneficial human health properties. Hydroxytyrosol (HT) has various biological activities, such as down regulation of the immunological response, preventing human erythrocytes from oxidative damage induced by hydrogen peroxide, anti-inflammatory, antithrombotic, and hypocholesterolemic effects [30]. hydroxytyrosol is also a potent inhibitor of MAO-B (monoamine oxidase). which makes it an hydroxytyrosol appropriate material for the treatment of Alzheimer's, Parkinson's and other disease [31]. HT can increase some enzymes which catalyse the phosphorylation of glucose such as hexokinase, pyruvate kinase and decrease enzymes which catalyse the dephosphorylation of glucose-6-phosphate to free glucose such as glucose-6-phosphatase and fructose-1,6-bisphosphatase, cause the closure of the ATP-sensitive potassium channels and increases the voltage-dependent calcium channel which plays a key role in insulin secretion HT also increases peripheral uptake of glucose [30]. This o-diphenol, like the majority of the olive phenols such as tyrosol, has been proven to be a potent scavenger of superoxide anion and hydroxyl radical [32]. HT was reported to be effective scavenger of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical as was established by Allouche et al. This antioxidant activity protects pancreatic cells from damage and death resulting in the increase of insulin secretion which decreases glucose level in plasma [30]. It occurs naturally in olive byproducts [32] (see Fig. 4).

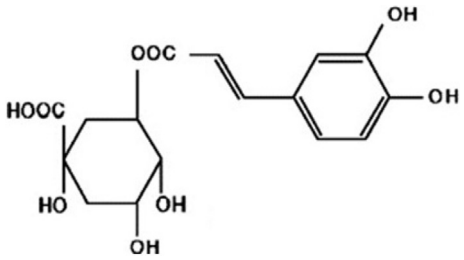

Fig. 3. Chemical structure of chlorogenic acid [27].

7. Ellagic acid

Eellagic acid (EA) (2,3,7,8-tetrahydroxy-chromeno [5,4,3-cde] chromene-5,10dione) is a phytochemical found in numerous fruits and vegetables and other plant foods. EA is known to have anti oxidative, anti-mutagen, anti-inflammatory and also has anticarcinogenic properties [34,35]. The possible mechanism of glucose lowering action may be through potentiation of insulin secretion from β-cells or due to enhanced transport of blood glucose to the peripheral tissue. In one study oral administration of ellagic acid to STZ-induced diabetic rats reduced the formation of glycosylated hemoglobin by virtue of its normoglycemic activity [35]. Ellagic acid was found to scavenge ROS (Reactive oxygen species) and RNS (Reactive nitrogen species) such as hydroxyl radicals, perxoyl radicals, NO_2 radicals, and peroxynitrite with rate constants comparable to those of many well-known antioxidants such as vitamin E and vitamin C [36]. Antioxidant activity of ellagic acid could be a result of direct scavenging of free radicals, sequestration of potential oxidants, regulation of enzyme activity, modulation of cell signaling, and regulation of gene expression [37]. One of the studies reports better protection of ellagic acid than vitamin E against oxidative stress. The protective effects of ellagic acid [38] are thus attributed to several factors including DNA binding, inhibition of the production of ROS, scavenging of ROS, and protection of DNA from alkylating injury. Ellagic acid is a polyphenol found in a many fruits and nuts such as raspberries, strawberries, walnuts, grapes, and black currants, carrot, tomato, blueberry, pecans, pomegranates, wolfberry and other plant foods [35,36,39] (see Fig. 5).

8. Conclusion

All these five phytochemicals have potent antidiabetic and antioxidant effects in different ways beside other properties like anti-inflammatory and anti-carcinogenic properties in ellagic acid, or like anti-angiogenic and apoptogenic activities in curcumin. Though there is many other phenolic compounds but we noticed

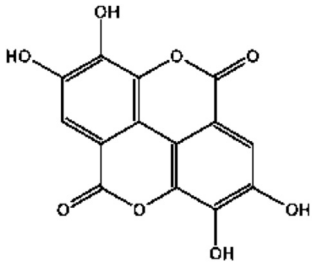

Fig. 5. Chemical structure of ellagic acid [40].

that there is only few data available about them in the field of diabetes and antioxidative activity and it could be said that almost only these five phenols were under related investigations. So we suggest more focused studies about phenols especially these five ones.

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