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Polyphenols and their protective effects including mechanisms of action against Diabetes mellitus

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Abstract

Diabetes mellitus, particularly type 2 diabetes (T2DM), represents a significant global health challenge characterized by insulin resistance and chronic hyperglycaemia. Recent research highlights the protective effects of dietary polyphenols, naturally occurring compounds found in various plant-based foods, against the development and progression of diabetes. This paper reviews the mechanisms through which polyphenols exert their antidiabetic effects, including the inhibition of amyloid aggregation, modulation of oxidative stress, reduction of inflammation, and enhancement of insulin sensitivity. Evidence from clinical trials and observational studies indicates that polyphenol-rich diets, especially those adhering to the Mediterranean dietary pattern, are inversely associated with T2DM risk. The ability of polyphenols to protect pancreatic β-cells from cytotoxicity and improve metabolic parameters underscores their potential as therapeutic agents in diabetes management. This review aims to consolidate current knowledge on the mechanisms of action of polyphenols and their implications for diabetes prevention and treatment.

Key words : Polyphenol, Type2 diabetes (T2DM), Dietary fibres.

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INTRODUCTION

Dietary polyphenols including phenolic acids, flavonoids, catechins, tannins, lignans,stilbenes, and anthocyanidins are widely found in grains, cereals, pulses, vegetables,spices, fruits, chocolates, and beverages like fruit juices, tea, coffee and wine. In recent years, dietary

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polyphenols have gained significant interest among researchers due to their potential chemopreventive/protective functions in the maintenance of human health and diseases.Natural products have been playing an important role in human health. Plants have been traditionally used to combat diseases in the medical traditions of different societies. Therefore, not surprisingly many modern drugs represent plant-derived substances for treating Type 2 diabetes (T2D) mellitus, with multiple prominent examples, such as acarbose, andrographolide, and galegine, which contributed to the discovery of biguanides (Figure 1). With so many successful records, the advantages of natural products-based drug discovery highlight biodiversity of resources, structural and chemical diversity, drug-likeness and biological friendliness, biocompatibility and biological validation, hints on efficacy and safety from application of traditional medicines, opportunities for use as scaffolds for chemical modifications to optimize potency, multi-targeted mechanism of action for diseases of complex etiology, and available to large-scale production by biotechnological approaches.

Phenolics are the intricate category of bioactive molecules produced by shikimate and acetate pathways that occur naturally. Almost all medicinal and edible plants contain phenolic compounds. Among the richest dietary sources of phenolic and polyphenolic compounds are fruits, spices, seeds, and vegetables. Moreover, certain beverages like tea, coffee, and wine contribute significantly to the daily intake of phenolics (Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). Due to their structural diversity and possessing therapeutic activities, researchers have focused on phenolic compounds exploring their use as medicinal agents. Compounds with one phenolic ring are generally classified as simple phenols, whereas those with more than one phenolic ring referred to as polyphenols (Figure 4). There are four major groups of phenolic compounds: simple phenols (designated as phenolic acid), lignans, stilbenes, and polyphenols (referred to as flavonoids). Among polyphenols, flavonoids represent the wide-ranging metabolites, which include flavonols, flavones, flavanones, isoflavones, and anthocyanins (Figure 3). Phenolic acids are the aromatic carboxylic acid with hydroxyl derivatives that have only one phenolic ring in their structure and are of two types, for example, hydroxybenzoic acid and hydroxycinnamic acid derivatives (Kondratyuk & Pezzuto, 2004). Caffeic, p-coumaric, ferulic, and sinapic acids are the hydroxycinnamic acid derivatives that are more abundant in

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

plant as compared to benzoic acid derivatives such as gallic acid, protocatechuic acid, and p-hydroxybenzoic acid.

MECHANISMS OF DIETARY POLYPHENOLS AS ANT DIABETIC AGENTS

Accumulated evidences from in vivo and in vitro investigations suggest a significant function of dietary polyphenols in the prevention and management of T2D through the insulin dependent approaches, for instance, protection of pancreatic islet β-cell, reduction of β-cell apoptosis, promotion of β-cell proliferation, attenuation of oxidative stress, activation of insulin signaling, and stimulation of pancreas to secrete insulin, as well as the insulin independent approaches including inhibition of glucose absorption, inhibition of digestive enzymes, regulation of intestinal microbiota, modification of inflammation response, and inhibition of the formation of advanced glycation end products (Table 1). Moreover, dietary polyphenols ameliorates diabetic complications, such as vascular dysfunction, nephropathy, retinopathy, neuropathy, cardiomyopathy, coronary diseases, renal failure, and so on.

Flavonoids

Flavonoids and extracts rich in flavonoids from coffee, guava tea, whortleberry, olive oil, propolis, chocolate, and cocoa have been widely studied as possible antidiabetic agents. Quercetin was the most widely investigated flavonoid in the literatures for the in vivo and cellular antidiabetic effects in animal and cell models (Shi et al., 2019), followed by kaempferol (Alkhalidy et al., 2018), luteolin (Sangeetha, 2019), myricetin (Li et al., 2017), and naringenin (Den Hartogh & Tsiani, 2019). Compared with these aglycones, flavonoid O-glycosides shown less antidiabetic potential (Xiao, 2017). However, flavonoid C-glycosides, such as vitexin, isovitexin, swertisin, apigenin 6-C-β-fucopyranoside, and apigenin 6-C-(2″-O-α-rhamnopyranosyl)-β-fucopyranoside, exhibited positive antidiabetic activity in hyperglycemic animals (Xiao et al., 2016). There is an increasing demand for new therapeutic agents that can control this metabolic disorder and at the same time bring less adverse health effects (Lv et al., 2019). In this sense, phenolic compounds are bioactive ingredients that can be considered as potential agents for diabetes management (Fig. 2). For example, flavonoids (including the

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

subclasses of flavones, flavonols, flavanones, flavanols, anthocyanidins, isoflavones, and flavanonols) have been reported to maintain the survival and function of pancreatic β-cells through molecular mechanisms that involve the reduction of oxidative stress (by increasing endogenous antioxidant capacity, less ROS accumulation and translocation of pro-inflammatory cytokines in β-cells), increased expression of anti-apoptotic genes (e.g., Bcl-2 protein), and reduced expression of pro-apoptotic genes (e.g., caspase-3 and caspase-8) and DNA damage, protecting them against autophagy, apoptosis, necroptosis and cell damage in hyperglycemic conditions (Ghorbani et al., 2019). Moreover, scientific evidence suggests that phenolic metabolites (derived from flavanol, flavan-3-ols, quercetin, and anthocyanins) and phenolic acids (e.g., ferulic, chlorogenic, and caffeic acids) can reduce ROS levels, inflammation and protein glycation, inhibit key enzymes related to carbohydrate metabolism and T2DM, increase glucose transporter 4 (GLUT 4) expression, and glucose uptake, in addition to activating pathways responsible for insulin signaling and secretion, thereby improving blood glucose levels (Chen, et al., 2019). More details on the mechanisms of action of dietary phenolic compounds will be discussed in the following topics.

Chemical agents that generate oxygen-free radicals like ionizing radiations and activated oxygen cause DNA damage which results in mutations, deletion, and similar lethal genetic effects. Oxidative DNA damage causes the development of various oxidative DNA lesions, which may trigger mutations (Halliwell and Gutteridge, 2015). Because of DNA disruption, base moieties and sugar become more vulnerable to oxidation, resulting in protein crosslinking, base degradation, and single-strand breakage (Zadák et al., 2009). Further, OS exerts deleterious effects on DNA leaformation of DNA lesions, which can result in genomic instability and consequently lead to cell death. The guanine (a base of DNA) is most susceptible to oxidation in cellular OS. In the presence of ROS, the oxidation of guanosine to 8-oxoguanosine (8-oxoG) takes place. The formation of 8-oxoG is the most common lesion in the DNA molecule. When 8-oxoG is inserted during DNA replication, it could generate double-strand breaks, which finally causes damage to DNA molecule (Aguiar et al., 2013).

Antidiabetic effects of dietary polyphenols.

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

After ingestion, the phenolic compounds are absorbed in the small intestine (5–10% of the total polyphenols ingested) and metabolized in the liver to methoxy, sulfated and/or glucuronidated metabolites by phase II enzymes prior entering the bloodstream. The chemically more complex phenolic compounds that are not absorbed in the small intestine (about 90–95%) reach the colon, where they are metabolized by the microbiota present in metabolites that are simpler to be absorbed. Colonic fermentation of these compounds also causes significant changes in the gut microbiota, in addition to increasing the production of short-chain fatty acids (SCFAs) that are absorbed by specific receptors present in colonocytes. Once in circulation, metabolites derived from phenolic compounds (by metabolism in the liver or gut microbiota) are distributed to various organs and tissues and can have several antidiabetic effects, including increased insulin secretion, inhibition of digestive enzymes and DPP-IV, decreased oxidative stress, protein glycation, and inflammation, improved insulin resistance, among others.

A randomized controlled trial found that a diet naturally rich in polyphenols improves glucose metabolism in individuals at high risk of diabetes (Bozzetto et al., 2015). A 4-week, double blind, randomized, placebo controlled trial involving 32 T2D patients showed that flavonoid-rich grape seed extracts significantly improved the biomarkers of inflammation, glycemia, and oxidative stress in the events of obese T2D subjects at high risk of cardiovascular (Kar, Laight, Rooprai, Shaw, & Cummings, 2009). A double-masked, randomized controlled trial found that the daily intake of flavanol-containing cocoa might improve the vascular function of medicated T2D patients (Balzer et al., 2008). A randomized, double-blind, placebo-controlled trial with 48 T2D patients revealed that a 12-week daily supplementation of PycnogenolR (125 mg), a French maritime pine bark extract rich in procyanidins and bioflavonoids, could increase diabetes control, reduce cardiovascular disease risk factors, and lower antihypertensive medicine use vs controls (Zibadi, Rohdewald, Park, & Watson, 2008). In a double-blind, 8-week randomized controlled study involving in 80 T2D patients, Brazilian green propolis (226.8 mg/day) rich in polyphenols and flavonoids was found to prevent T2D patients from worsing developments in blood uric acid and estimated glomerular filtration rate (Fukuda et al., 2015). A randomized, double-blind, placebocontrolled trial (34 subjects) showed that the supplementation of acacia

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

polyphenol (250 mg/day) might improve glucose homeostasis in nondiabetic subjects with impaired glucose tolerance (Ogawa, Matsumae, Kataoka, Yazaki, & Yamaguchi, 2013). Coffee polyphenols can improve peripheral endothelial function following glucose loading in healthy male adults (Ochiai et al., 2014). Coffees with different contents of chlorogenic acids did not show different degrees of influence on glucose or insulin responses in healthy humans (Rakvaag & Dragsted, 2016). Red wine polyphenols were found to have a beneficial effect on insulin resistance and lipoprotein plasma concentrations in a randomized clinical trial involving 67 men with high cardiovascular risk (Chiva-Blanch et al., 2013). A whortleberry extracts rich in anthocyanins significantly lowered the levels of fasting blood glucose, 2-hr postprandial glucose, and HbA1c in a randomized, double-blind, placebo-controlled clinical trial, consisting of 37 T2D patients (Kianbakht, Abasi, & Dabaghian, 2013).

Isoflavones

Significant evidence from epidemiological investigations has shown that soybean isoflavones intake is linked to a lower risk of diabetes (Konishi et al., 2019). Soy isoflavones perform hypoglycemic effects in Goto–Kakizaki diabetic rats via suppression of carbohydrate digestion and glucose uptake in small intestine (Jin et al., 2018) and delay the process of renal interstitial fibrosis in diabetic nephropathic rats (Liu et al., 2018). Among soy isoflavones, puerarin, the 8-C-glucoside of daidzein, showed best hypoglycemic effects via improving insulin resistance and sensitivity, protecting pancreatic beta-cells, exerting ant inflammation activity, decreasing oxidative stress, and inhibiting Maillard reaction and advanced glycation end products formation (Chen et al., 2018; Chen, Yu, & Shi, 2018).

Moreover, puerarin ameliorates diabetic complications, such as cardiovascular complications, diabetic nephropathy, retinopathy, neuropathy, and so on. Genistein benefits type 2 diabetes via remarkably ameliorating hyperglycemia (Fu et al., 2012; Rockwood et al., 2019), enhancing beta-cell proliferation and reducing apoptosis (Gilbert & Liu, 2013), ameliorating cardiac inflammation and oxidative stress (Gupta et al., 2015), Biochanin A showed hypoglycemic effect on streptozotocindiabetic rats (Harini, Ezhumalai, & Pugalendi, 2012).

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

Biochanin A significantly reduced insulin resistance, improved inulin sensitivity and lipid profile, and attenuates neuropathic pain in diabetic rats (Chundi et al., 2016). Formononetin treatment reduces insulin resistance and attenuate hyperglycemia in T2D, which may be due to increasing expression of SIRT1 in pancreatic tissues (Oza & Kulkarni, 2018). Methylated isoflavones look like they exhibit better antidiabetic effect than nonmethyl forms. However, it needs further investigation in animals and human studies.

CATECHINS

Catechins are natural polyphenols present in edible and medicinal plants, especially in tea leaves (Khan & Mukhtar, 2018). Catechins show a very low bioavailability. After consumption of a single cup of tea, plasma concentrations of catechins rinse quickly reaching a maximum after 2 hr, to then gradually decrease to reach the basal levels within 8 hr. Pharmacokinetic studies demonstrated that in human cells p-glycoprotein is responsible for both uptake and excretion of catechins (Vaidyanathan & Walle, 2003); however, due to the high individual variability existing between humans, the pharmacokinetics of catechins may change considerably from person to person (Ullmann et al., 2003). There is a large agreement between researchers in sustaining that catechins have a positive impact on human health. Evidence suggested that the regular consumption of catechins could contribute to prevent gain of weight or the onset of chronic disease such as T2D or metabolic syndrome (Thielecke al important hydroxycinnamic acids, such as cinnamic acid, pcoumaric acid, ferulic acid, caffeic acid, chlorgenic acid, and rosmarinic& Boschmann, 2009; Park, Bae, Im, & Song, 2014). In particular, catechins contribute to reduce glycaemia, enhance insulin sensitivity, decrease blood lipids, and reduce white fat al important hydroxycinnamic acids, such as cinnamic acid, pcoumaric acid, ferulic acid, caffeic acid, chlorgenic acid, and rosmarinicdepots.

Cinnamic acid improved glucose intolerance and insulin resistance in streptozotocin (STZ)-induced diabetic rats (Kasetti, Nabi, Swapna, & Apparao, 2012). Ferulic acid reduced blood

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

glucose level and increased blood insulin level in several diabetic animal models (Jung, Kim, Hwang, & Ha, 2007; Ohnishi et al., 2004). Ferulic acid also increased glucokinase activity (Jung et al., 2007) and decreased glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities in liver (Son, Rico, Nam, & Kang, 2011). Caffeic acid has been studied extensively in experimental diabetes and related complications. Caffeic acid shows hypoglycemic effects (Celik, Erdogan, & Tuzcu, 2009; Jung, Lee, Park, Jeon, & Choi, 2006), improves insulin level (Cy, Mc, Kc, & Mc, 2010), and enhances glucose intolerance (Bezerra et al., 2012) in diabetic animals.

Chlorogenic acid is the major phenolic components in coffee, which evidently reduces the risk of type 2 diabetes. Chronic dietary chlorogenic acid consumption attenuated cardiovascular, liver, and metabolic changes (Bhandarkar, Brown, & Panchal, 2019). Chlorogenic acid was found to attenuate diabetic complications in animals such as retinopathy via inhibiting retinal neoangiogenesis (Mei et al., 2018) and sensorineural auditory function (Hong, Nam, Woo, & Kang, 2017). However, chlorogenic acid could lower the fasting plasma glucose and HbA1c levels during late diabetes in db/db mice (Jin et al., 2015), and there is no sufficient evidence that decaffeinated coffee-enriched chlorogenic acid can control blood glucose in animals (Faraji, 2018). Chlorogenic acid poorly inhibits carbohydratedigesting enzymes (Nyambe-Silavwe & Williamson, 2018) and weakly impacted the fasting blood glucose level and blood glucose levels in the oral glucose tolerance tests in kk-[a.sup.y] mice (Igarashi, Takahashi, & Sato, 2017). Chlorogenic acid supplementation in a high-fat diet does not protect against features of the metabolic syndrome in dietinduced obese mice (Mubarak, Hodgson, Considine, Croft, &Matthews, 2013).

Caffeoylquinic acids:

PTP1B is one the most promising targets to improve insulin sensitivity, and overcome insulin resistance in peripheral tissues (liver, muscle, and adipocytes) (Eleftheriou, Geronikaki, & Petrou, 2019). Interestingly, recent studies demonstrated that chlorogenic acid and some caffeoylquinic acid derivatives behave as noncompetitive inhibitor of PTP1B: among all

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

caffeoylquinic acids resulted the most potent inhibitor, showing a Ki value of about 15 micromolar (Chen et al., 2014; Zhang et al., 2018). These data suggest that caffeoylquinic acids could be used to improve insulin sensitivity in obese or T2D subjects. In keeping with this hypothesis, it has been reported that treatment with chlorogenic acid enhances glucose uptake in both insulin-sensitive and insulin-resistant adipocytes (Alonso-Castro, Miranda-Torres, González-Chávez, & Salazar-Olivo, 2008). Finally, studies conducted on human volunteers showed that the long-term assumption of coffee or extracts rich in caffeoylquinic acids reduces levels of blood glucose, increases the insulin response (Reis, Dórea, & da Costa, 2018), attenuates hepatic insulin resistance (Lecoultre et al., 2014), reduces serum lipids, and favors a reduction of body weight (Martínez-López, Sarriá, Mateos, & Bravo-Clemente, 2019). Together, these evidences support the hypothesis that caffeoylquinic acids have a deep impact on energetic metabolism of humans and can explain why the extracts rich in these compounds are recommended by traditional medicine for treatment of diabetes and obesity (Spínola & Castilho, 2017; Xie et al., 2019).

Anthocyanidins:

Anthocyanidins have a phenolic hydroxyl structure and are a class of hydroxyl donors with strong free radical scavenging ability. Anthocyanidins could reduce blood glucose by enhancing the antioxidant ability of bio-organisms through upregulating superoxide dismutase (SOD), lowering serum malonic dialdehyde, and inhibiting increasing thiobarbituric acid reactive substances (Roy, Sen, & Chakraborti, 2008; Tsuda, Horio, & Osawa, 1999). In vitro experiments indicated that cyanidin-3-glucoside protected cells from high glucose-induced oxidative stress by activating of glutathione synthesis (Zhu et al., 2012). Islet β cells are very sensitive to oxidative stress due to low expression of antioxidant enzymes such as CAT, SOD, and GPx in islets (Evans, Goldfine, Maddux, & Grodsky, 2003). Anthocyanin-rich mulberry extract exerted oxidative stress on islet cells against hyperglycemia through AMPK/ACC/mTOR pathway (Yan & Zheng, 2017). Anthocyanidins could improve insulin resistance by regulating blood lipid through reducing the levels of cholesterol, triglycerides, and low-density cholesterol and increasing the level of apolipoprotein and high-density cholesterol (Shi, Loftus, McAinch, & Su, 2017). Anthocyanidin-enriched bilberry extracts improved insulin resistance in KK-Ay mice, and

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

reduced total cholesterol and triglycerides in liver and serum (Takikawa, Inoue, Horio, & Tsuda, 2010). Pro-inflammatory factors such as TNF-α and IL-6 were found associated with insulin resistance (Guo et al., 2012). Studies also shown that Cyanidin-3-glucoside inhibited 3T3-L1 cell adipocytes, activated insulin pathway via FoxO1, and inhibited TNF-α-mediated insulin resistance (Guo et al., 2012). Anthocyanins promoted insulin secretion in many ways (Rosanska & Regulska-llow, 2011). Cyanidin-enriched purple potato extract promoted insulin secretion by upregulating the expression of intracellular Ca2+ signaling pathway and glucose transport-related gene (Glut2) in mouse islet beta cells (INS1) (Sun, Du, Navarre, & Zhu, 2018). Anthocyanidins (delphinidin 3-arabinoside) in fermented berry beverages regulated DPPIV and its substrate GLP-1, increased insulin secretion, and upregulated mRNA expression of insulin receptor-related genes (Johnson & Mejia, 2016). Delphinidin 3-rutinoside could induce GLP-1 release via a calcium-dependent kinase pathway (Kato, Tani, Terahara, & Tsuda, 2015).

The most important findings from our study suggest that the intake of polyphenols may modulate the FG level and weakly affect the HbA1c amount. As it was shown above, total polyphenol consumption influences FG but not significantly. Nevertheless, in the group with high intakes of flavonoids (the main group of polyphenols), the glucose concentration was significantly lower compared to the group characterised by low flavonoid intake . The analysis of the association showed that polyphenols, especially flavonoids, influence the fasting glucose concentration; a negative association was observed between glucose level and total polyphenol, flavonoid, flavan-3-ol and stilbene intake .Anthocyanins and procyanidins are considered as highly bioactive compounds and present in fruits, bark, leaves, and seeds of many plants and plant-derived food. Nabavi and coworkers reviewed the benefits of anthocyanins for diabetic retinopathy.The evidence suggests that the antioxidant and other bioactivities of anthocyanins can mitigate vision loss and retinal degenera-tion in diabetes. It is still unclear on the beneficial role of anthocyanins in diabetic patients who suffered from retinal complica-tions. Anthocyanins have minimal adverse effects, however, and could be good candidates for future clinical trials. González-Abuín et al. focused on the healthy protective effects of procyanidins on type 2 diabetes and insulin resistance. Procyanidins were found to improve the damage induced by the diet, thus improve glycemia and insulin sensitivity. Human studies, although limited, further

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

support the hypoglycemic effect of procyanidins. Procyanidins have been found to target several tissues involved in glucose homeostasis. In insulin-sensitive tissues, procyanidins modulate glucose uptake and lipogenesis and improve their oxidative/inflammatory state, the disruption of which plays a key role inT2DM development. In pancreas, procyanidins modulate insulin secretion and production and -cell mass.

Curcumin

Curcumin is a natural compound extracted from the root of Curcuma Longa and is the main component of the Indian curry spice. Curcumin has been consumed in the traditional Asian medicine for centuries because of its anti-inflammatory properties. Curcumin has also an-tioxidant and anticarcinogenic effects (5-7). Its anti-cancer activity is mainly attributable to the inactivation of hypoxia-inducible factor-1(HIF-1), as curcumin is known to downregulate HIF-1α (8) and HIF-1β (9) and inhibit downstream actions, e.g. angiogenesis mediated by HIF-1. Also, it is able to selectively kill tumor cells or prevent tumorigenesis through interfering with many cellular pathways (6, 10). It represses nuclear factor-κB (NF-κB), inhibits adipogenic transcription factors and the cell cycle, and induces apoptosis (11-13). In colorec- tal cancer, curcumin treatment upregulates p53 expression (14). It has been reported that curcumin inhibits TNF-α-induced expression of Interleukin-1 beta (IL-1β),IL-6, and tumor necrosis factor (TNF-α) in human keratinocytes. It enhances the secretion of adiponectin (15), inhibits insulin-regulated glucose transporter 4 (GLUT4) translocation and glucose transport (16, 17). Some studies demonstrate that 10–25 μM of curcumin efficiently inhibited the differentiation of mouse adipocytes. In concentrations of 10–50 μM, curcumin is able to activate AMP-activated protein kinase (AMPK)(18) and it can also inhibit the activation of MAPK pathway, c-Jun N-terminal kinases (JNK), p38MAPK, and extra cellular signal-regulated kinases (ERK) in adipocytes (19).

Genistein

The isoflavone genistein is a naturally occurring phytoestrogen, which is particularly highly concentrated in soy and soy-derived products; its possible suitability as a pharmacological agent has been studied, as it has been illustrated that people in Asia consuming large amounts of genistein-rich soy products are seldom affected by prostate or breast cancer (104, 105) and Type

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

2 diabetes (106). In hypoxic conditions, genistein has been shown to suppress the HIF1α expression, accumulation, and activation of ERK (107, 108). Also, genistein seems to provide a protective effect on myocardial and endothelial cells, as it activates the exocytosis of the cardioprotective neuropeptide calcitonin gene-related peptide. This is due to vanillin receptor 1(VR1)-mediated action, of which genistein is supposed to be a direct activator (109), apart from capsaicin and gingerol. , the effect of genistein on differentiation of adipocytes has been illustrated with inconsistent results; this is in part due to contradictory actions of genistein with respect to applied concentrations (110, 111, 113-119). In a study, streptozotocindiabetic rats that received a daily intraperitoneal injection of 1 mg/kg bw showed a hypoglycemic effect (120). In a study on mice, 2 and 4 g genistein/kg diet significantly decreased fat pads, cholesterol, and lipid levels. Moreover, it inhibited mRNA expression of PPARγ, leptin, and TNFα and also increased mRNA expression in case of PPARα, AMPK, and adiponectin in adipose tissue (121). Furthermore, it enhanced the expression of genes involved in fatty acid oxidation, and at the same time, activated expression of UCP2, which mediates proton leakage by uncoupling ATP synthesis. This lowered metabolic efficiency may also account for the reduced fat accumulation and weight gain in animals receiving a daily genistein dose of about 200, 400, or 800 mg/kg of the body weight (Pandey et al., 2010). Similar to resveratrol, genistein administration decreased the ATP level in adipocytes (Pandey et al., 2010). Recent clinical trials on genistein in males showed an increase in adiponectin levels and a decrease in cholesterol and insulin levels, with doses that can easily be obtained by a soy rich diet. Table 6 displays recent clinical trials testing genistein with respect to diabetic and inflammatory markers.

Adipocytes are the place for energy storage and they produce cytokines including interleukin IL-1β, IL-6, TNF-α, MCP-1, leptin, adiponectin, and many other molecules; thereby, they are referred to as adipokines. In the context of inflammation, the adipose tissue is infiltrated through macrophages, and it also releases proinflammatory mediators, produces reactive oxygen species, and stimulates T-cell responses for successful defense against invading organisms.

DIETARY POLYPHENOLS, THEIR CHEMISTRY AND SOURCES

Polyphenols are found naturally in fruits and vegetables such as cereals, pulses, drtea, cocoa, coffee and so on (Arts and Hollman, 2005; Scalbert et al., 2005). Polyphenols are classified into

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

different groups depending on the number of aromatic (phenolic) rings they contain and the structural elements that connect these rings. They are broadly grouped into phenolic acids, flavonoids, stilbenes and lignans (Khan et al., 2021). Plant derived polyphenolic compounds (for example, phenolic acids and flavonoids) occurs in conjugated forms with one or more sugar residues (as glycosides) bound to hydroxyl groups through direct linkages of the polysaccharide or monosaccharide-like sugar to an aromatic carbon (Rudrapal and Chetia, 2017). It is naturally bound to a variety of other molecules, including carboxylic and organic acids, lipids, amines, and other phenolic compounds (Kondratyuk and Pezzuto, 2004)ied legumes, spinach, tomatoes, beans, nuts, peppermint, cinnamon, pears, cherries, oranges, apples, red wine, tea, cocoa, coffee and so on (Arts and Hollman, 2005; Scalbert et al., 2005). Anthocyanidins are the bright coloured (blue, red, or purple pigments) flavonoid compounds found in the flowers, fruits and leaves etc.

Diabetes Mellitus Abnormality in glucose metabolism leads to hyperglycemia and consequently diabetes mellitus (type-1 and type-2). Apart from co-morbidities like heart disease or stroke, chronic complications may develop in diabetes such as diabetic retinopathy affecting eyes cause blindness, nephropathy altered renal functions, and neuropathy causing nerve damage and numbness/paralysis (Rizvi and Zaid, 2001; Rizvi and Zaid 2005; Junejo et al., 2017; Junejo et al., 2018; Junejo et al., 2020a; Junejo et al., 2020b; Hussain et al., 2021; Junejo et al., 2021). Apigenin derivative possesses strong antidiabetic activity extending protection against the variations throughout OS in diabetes (Junejo et al., 2021). Quercetin decreases lipid peroxidation and inhibits cellular oxidation in diabetes (Pandey and Rizvi, 2009). Resveratrol prevents cytotoxicity and OS caused by excessive glucose levels. Resveratrol decreases diabetes-induced kidney alterations (diabetic nephropathy) and thereby increases renal disorder and OS in diabetic rats. Resveratrol reduces secretion of insulin and deferrers insulin resistance onset which may be due to the inhibition of K+ ATP and K+ V channels in β cells (Chen et al., 2007; Oyenihi et al., 2016). The polyphenols of Hibiscus sabdariffa weaken diabetic nephropathy in terms of serum lipid profile and kidney oxidative markers (Lee et al., 2009). H. sabdariffa also contains flavonoids, protocatechuic acid, and anthocyanins..

CONCLUSION :

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

Food phenolics are gaining importance in research as they have the potential to improve human health. Over 8,000 polyphenols have been reported from plants, and several hundreds of dietary polyphenols have been found in foods. Owing to their potent antioxidant capacity because of the presence of hydroxyl groups in their structures, polyphenols can effectively scavenge ROS and thus fight against OS induced pathological conditions or human diseases. Evidence from diverse in vitro studies discussed here supports that dietary sourced polyphenols plays a potential protective role in the prevention of neurodegenerative diseases, CVDs, diabetes, cancer, inflammation-related diseases, and infectious illness. However, prospective further research with adequate pre-clinical and clinical investigations could lead to the development dietary polyphenolic compounds as potent therapeutic candidates against various chronic human diseases.

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ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 06, 2022

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