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Antidiabetic potential of natural phytochemical antioxidants

Md. Fahim Ahmad[1], Inamur Rahman[1], Nida Naseem[1], Nazia Imam[1], Hina Younus[1], Haseeb Ahsan[2], Waseem A. Siddiqui[1,*]

[1]Interdisciplinary Biotechnology Unit, Faculty of Life Sciences, Aligarh Muslim University, Aligarh-202002, India
[2]Department of Biochemistry, Faculty of Dentistry, Jamia Millia Islamia, New Delhi – 110025, India

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Abstract: Diabetes mellitus is a chronic metabolic ailment caused due to complex interactions of genetic and environmental factors (dietary and lifestyle). It causes remarkable morbidity and mortality due to microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (heart attack, peripheral vascular disease, and stroke) complications. Treatment of microvascular complications focuses on blood sugar control. Although preventing macrovascular complications requires correcting classical cardiovascular risk factors that involve insulin resistance (metabolic) syndrome. The use of traditional drugs adopts several antidiabetic remedies. These drugs are effectivebecause most of these drugs are taken by patients for their entire life and causeseveral adverse effects like diarrhoea, abdominal distention, and flatulence emanate by intaking these drugs. Due to these restrictions,there is a need to explore management strategies in medicinal plants with cost-effective antidiabetic potentials and fewer or negligible side effects. Applying traditional medicine for diabetes and its associated complications has received increasing attention. This review explores the antidiabetic potential of some commonly and extensively used phytochemicals obtained from traditional medicinal plants.

Keywords: Diabetes mellitus; microvascular; macrovascular; diabetes management; conventional drugs; phytochemicals; phytonutrients

1. Introduction

Diabetes mellitus is a major metabolic disorderlinked to morbidity and mortality due to chronic complications (Jia et al., 2013). Diabetes is categorized as type 1 and type 2 diabetes mellitus. Diabetes mellitus type 1,also called as juvenile-onset diabetes orinsulin-dependent diabetes, is immune-mediated.In this case, cells of the own body cause damageto beta cells of pancreatic islets, which cannot produce insulin from the pancreas.In contrast, Type 2 diabetes mellitus (T2DM) or adult-onset diabetes (formerly considerednon-insulin-dependent diabetes) is occurred due to impaired insulin secretion and resistance to insulin action (Holt, 2004). T2DM is a progressive and complex metabolic disorder risingglobally (Olokoba et al., 2012). Worldwide,more than 170 million individuals are affected by type 2 diabetes mellitus (Zimmet et al., 2001).T2DM is affected by severalfactors related to lifestyle. These are lack of physical activity, poor diet, cigarette smoking, and massive alcohol consumption (Hu et al., 2001). Obessed and high weight people are more prone to type 2 diabetes mellitus (Colditz et al., 1995).

* Corresponding Author: wasiddiqui01@gmail.com

Recent studies and surveys showed that diabetes mellitus is a significant and escalating global health burden and is likely to grow in the coming decades (Guariguata et al., 2014). In diabetes mellitus, the absence of active insulin causes disablement of uptake and storage of glucose for energy purposes (Ayeleso et al., 2016). The main characteristics are abnormal insulin secretion and carbohydrate and lipid metabolism derangement,diagnosed as hyperglycemia (Naziroglu et al., 2005). The pathology and complications of diabetes mellitus are significantly affected by oxidative stress (Wolff, 1993). Oxidative stress is expounded as the increase in the formation of incomplete elimination of highly reactive molecules like reactive oxygen species (ROS) and reactive nitrogen species (NOS) (Maritim et al., 2002). Both ROS and RNS can oxidizecytoplasmic proteins, nucleic acids, and lipids. The onset of T2DM is closely related tooxidative stress, primarily through oxidation, non-enzymatic glycation of proteins, and oxidative degradation of these glycated proteins (Rosen et al., 2001). The major macrovascular complications include stroke, heart attack, and peripheral vascular disease. In contrast, major microvascular complications are nephropathy (kidney disease), neuropathy (neural damage) and retinopathy (eye disease) (Forbes et al., 2013). Thus, diabetes covers a wide range of diverse conditions. Therefore, treatment is required to stop the outbreak and development of these complications.

1.1. Therapies and medications for Diabetes Mellitus type 2

Studies have shown that strict metabolic control can help delay or prevent the progression of diabetic complications (Ohkubo et al., 1995). Large randomized trials of patients with T2DM observed that glycaemic control retards the onset and the development of microvascular complications such as nephropathy, neuropathy and retinopathy (Ismail-Beigi et al., 2010; Shobana et al., 2005). Controlled diet, exercise, and weight loss are recommended non-pharmacological therapy to lower blood glucose levels. It is accompanied by several oral drug therapies that have anti-hyperglycaemic effects. These drugs are given either as a monotherapy or in combination. Eight distinct drug classes, each with a unique mechanism of action, have been recognized: insulin, biguanides, α-glucosidase inhibitors, thiazolidinediones, sulphonylureas, meglitinides GLP-1 agonists, and gliptins.

Insulin therapy: Regular administration of insulin injections suppresses glucose production and enhances glucose utilization.

Biguanides: The precise mechanism of action of metformin, a commonly used biguanide,has not yet been dissected, but it predominantly reduces glucose production in hepatocytes in the presence of insulin (Inzucchi et al., 1998; Hundal et al., 2000). It is therefore considered an insulin sensitizer.

α-Glucosidase Inhibitors (AGIs): The glucosidase enzyme in the brush border intestinal epithelium helps breakdisaccharides and more complex sugar moieties. The AGIs' competitively inhibiting this glucosidase enzyme retard carbohydrate absorption in intestinal epithelia and attenuate postprandial glucose excursions (Goke and Herrmann-Rinke, 1998; Lebovitz, 1998).

Thiazolidinediones: It is a peroxisome proliferator-activated receptor-gamma ligand that enhances insulin-stimulated glucose absorption by skeletal muscle cells (Frias et al., 2000; Petersen et al., 2000; Maggs et al., 1998; Nolan et al., 1994). Therefore, these leads help reduce insulin resistance in peripheral tissues.

Sulphonylureas: Sulphonylureas (SUs) are known as insulin secretagogues. The SUs bind to the surface receptors on pancreatic β-cells leading to the closure of voltage-dependent potassium-ATP channels and causing calcium entry into the cell and thus insulin secretion (Zimmerman, 1997). Therefore, SUs help release insulin at reduced glucose thresholds than average. They aid in the reversal of the attenuated insulin secretion that characterizes T2DM.

Meglitinides: These short-acting antidiabetic agentsare essential in lowering postprandial hyperglycemia and lessening the danger of hypoglycemia. Similar to sulfonylureas, they have an affinity for an ATP-dependent K^+ (K^+- ATP) channel on the cell membrane of pancreatic β-cells.

Glucagon-like peptide-1 (GLP-1) agonists: It is an incretin hormone secreted from the gut after a meal. Excitation of the GLP-1 receptor helps enhanced insulin discharge with respect to glucose. Thus, unlike sulphonylureas, it prevents hypoglycemia (Rocca and Brubaker, 1999). Moreover, it slows gastric emptying, obstructs inappropriate post-meal glucagon secretion from the liver, and reduces food intake.

Gliptins-DPP-4 inhibitors: The oral DPP-4 inhibitors generally increase GLP-1 and GIP concentration by interfering with the degradation of the enzyme DPP-4 active site. Their primary effectiveness is controlling insulin and glucagon release without increasing weight.

Table 1. Anti-diabetic drugs and their associated pathophysiological/pharmacological effects

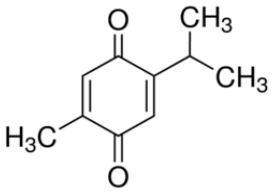
S. No.	Drug Class	Name of drugs	Molecular targets	Site(s) of action	Adverse effect	References
1.	Insulin	Insulin injection	Insulin receptor	Liver, muscle, fat	Hypoglycemia, weight gain	Lebovitz, 2011
2.	Sulphonylureas	Glibenclamide, glipizide, glimepiride	SU receptor/ K^+ ATP channel	Pancreatic β cell	Hypoglycaemia, weight gain	Sola et. al., 2015
3.	Biguanides	Metformine, phenformin	Unknown	Liver (muscle)	Gastrointestinal disturbances, lactic acidosis	Scheen and Paquot, 2013
4.	α-glucosidase inhibitors	Acarbose, miglitol	α-glucosidase	Intestine	Gastrointestinal disturbances	Lebovitz, 1997
5.	Thiazolidinediones	Pioglitazon, rosiglitazone	PPARγ	Fat, muscle, liver	Weight gain, oedema, anaemia	Niemeyer and Janney, 2002
6.	Meglitinides	Repaglinide, nateglinide	SU receptor/ K^+ ATP channel	Pancreatic β cell	Hypoglycaemia, weight gain	Wu et. al., 2017
7.	GLP-1 agonists	Semaglutide, lixisenatide	GLP-1 receptors	Pancreatic β cell	Increased risk of pancreatic cancer	Filippatos et. al., 2014
8.	Gliptins	Sitagliptins, linagliptins, tenegliptins	DPP-4 enzymes	Cell surface	Nasopharyngitis, headache, nausea, heart failure	Seshadri and Kirubha, 2009

However, these therapies have limited efficacy and tolerability despite being costly and accompanied byseveral adverse events. Weight gain is the primary cause of concern for most of these treatments. Several other approaches are also linked with the incidents of hypoglycemiaand gastrointestinal

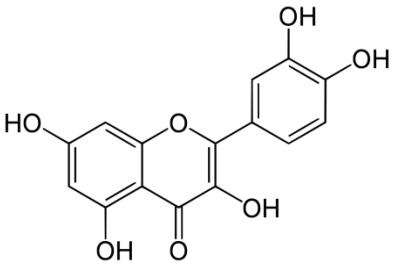
disturbances - patients who are initially responsive to sulphonylurea become obstinate to treatment over time. Moreover, existing therapies are insufficient to directly affect the other late-hour complications of diabetes (for example, neuropathy and retinopathy) that burden persons with this debilitating complex metabolic disease. Therefore, there is a need for newer and cheaper approaches that can be used against diabetes with lesser or no adverse effects.

1.2. Phytochemicals

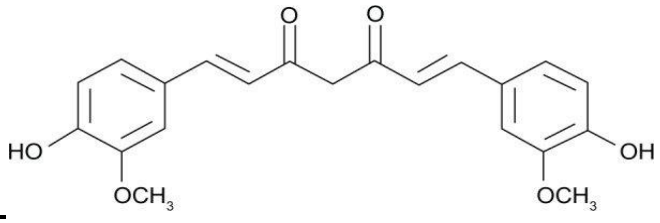
Several plant-derived active compounds have gained attention as effective candidates for diabetic treatment. Dietary antioxidants can be a therapeutic strategy to lower oxidative stress and prevent related diabetic vascular complications. In this regard, phytochemicals are potent antioxidants and antihyperglycemic compounds. It works through several metabolic pathways that directly or indirectly affect our body's glucose level. They affect glucose metabolism pathways via the alimentary canal, increasing insulin release and efficacy (Prabhakar and Doble, 2008). Scientific and laboratory studies have shown that plants incorporate many substances possessing antioxidant activity (Chanwitheesuk et al., 2005). Phytochemicals that offer antioxidant properties include cinnamic acids, lignans, flavonoids,coumarins, monoterpenes, diterpenes, triterpenes, phenylpropanoids, and tannins. Injury to plants and mammalian cells is linked with the triggering of lipoxygenases that mediate the generation of hydroperoxides of polyunsaturated fatty acids (PUFA). These hydroperoxide radicals may combine with fatty acids leading to the formation of dioxoenes, considered plant defence compounds. Plant oxidative mechanisms may explain the plentitude of antioxidant compounds identified in plant tissue (Larkins and Wynn, 2004). Therefore, plants, predominantly those with solid and high antioxidant compounds, play a pivotal role in improvingoxidative stress disorders, including diabetes mellitus. This review has mentioned a few established phytochemicals used to enhance diabetic complications in several experimental and clinical models.



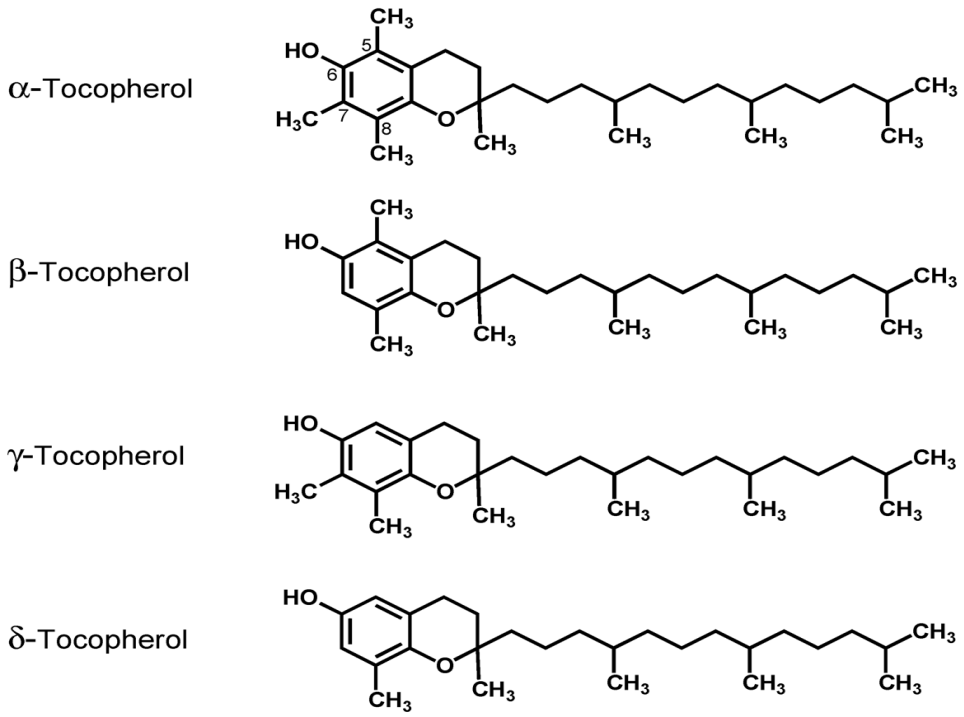
A. Thymoquinone



B. Quercetin



C. Curcumin



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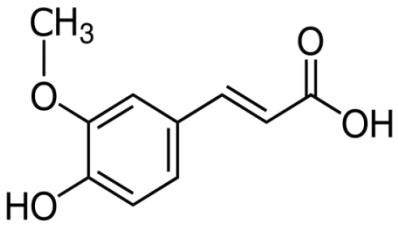
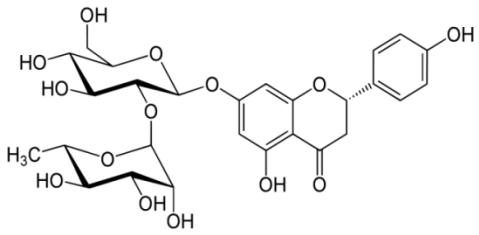
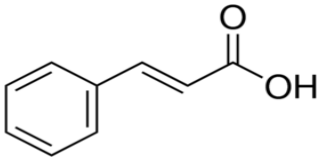


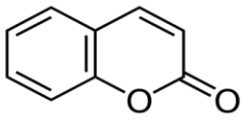
E. Ferulic



F. Naringin



G. Cinnamic



H. Coumarin

Figure 1. Structures of some phytochemicals

Treating diabetes mellitus with synthetic drugs is associated with potential side effects and economic burden on the patient. The utility of dietary supplements, botanicals and nutraceuticals has become an alternative for preventing and alleviating the complications of diabetes mellitus. Nutrients and phytochemicals are essential in managing diabetes mellitus with less tolerability and side effects. Vitamins are complex organic substances required by the body in minute quantities. Among different classes of vitamins, vitamin E is a fat-soluble vitamin, an antioxidant, detoxifying free radicals directly (Maritim, 2002). The antioxidant properties of vitamin E can prevent and treat numerous health-associated problems. Phytochemicals derived from medicinal plants confers an excellent opportunity to develop new therapeutics for diabetes mellitus (Gaikwad et al., 2014). The use of phytochemicals may retard the growth of diabetic complications and regulate metabolic

abnormalities through various mechanisms (Mukherjee et al., 2006). Among those phytochemicals, flavonoids are naturally exhisting polyphenolic compounds found in abundance in fruits and vegetables that constitute a large proportion of the plant kingdom (Martin and Christy, 2010). Structurally, two aromatic rings (A and B rings) are present in flavonoids, connected by a three-carbon chain that constitutes an oxygenated heterocyclic ring (C ring). Itcanrummage free radicals and chelate metals (Arts and Hollman, 2005). Immense research on natural flavonoids with antihyperglycemic activities has created a new way with promising progressive approaches in diabetic research. As it is essential to look for an economical and therapeutically effective treatment with fewer side effects, scientists have found more natural antidiabetic agents targeting multiple factors of diabetes and its complications. Among several antidiabetic phytochemicals, this review paper presents the highlight and therapeutic potential of ferulic acid, curcumin, thymoquinone, tocotrienol, Naringin and quercetin used for the cure of diabetes mellitus and its associated complications.

Thymoquinone.

Thymoquinone (TQ) is the main biologically active element of *Nigella sativa*of the family *Ranunculaceae*. It has been implicated as a folk medicine to cure diabetic features and lessen blood glucose (Ali and Blunden, 2003). *N. sativa* has been shown to elevate insulin secretion and insulin sensitivity (Le et al., 2004; Rchid et al., 2004). TQ has been found to reduce hepatic glucose production (Fararh et al., 2005) and protection of β-cells from oxidative stress after streptozotocin (STZ) treatment (Sankaranarayanan and Pari, 2011). Thymoquinone has protective effects against oxidative stress, inflammation, coronary artery diseases, respiratory failures, hypertension, urinary system failures, diabetes, neurodegenerative diseases and apoptosis. The anti-inflammatory effect of TQ is related to its inhibitory effects on cyclooxygenase and 5-lipoxygenase, and its antioxidant effect is associated with its property of scavenging the reactive oxygen species (ROS) (Nagi and Mansour, 2000). TQ access to subcellular compartments by penetrating physiological barriers exhibits the radical scavenging effect (Badary et al., 2003; Daba and Abdel-Rahman, 1998). TQ also reacts with glutathione (GSH), NADH, and NADPH, resulting in a reduced form of TQ, i.e., glutathionyl-dihydro-thymoquinone combats with free radicals (Khalife and Lupidi, 2007 and 2008).

TQ comprise of the enol, the keto and its mixtures forms. The major form is keto and is responsible for the pharmacological effects of TQ.When taken orally, TQ is metabolizedin liver by the help of enzyme DT-diaphorase (quinine reductase), changing TQ into a reduced form (Alkharfy et al., 2015).TQ has antidiabetic properties as it protects the β-cells from injury by decreasing ROS (Al-Trad et al., 2016). In STZ induced diabetic rats TQ showed the protective potential against hyperglycemia and decreases the activation of the COX-2 enzyme in the β-cells and MDA levels. In contrast, it increases the SOD (Superoxide Dismutase) in the pancreatic tissue of diabetic rats (Al-Wafai, 2013). Itis shown that during gestation and lactation of diabetic mice, supplementation of TQ (20 mg/kg bwt/d, p.o.)protected their offspring from developing diabetes and its complications by lowering the levels of blood glucose, free radicals and plasma proinflammatory cytokines (IL-1b, IL-6, and TNF-a). It also helps in the restoration of a number of circulating lymphocytes, the multiplication of superantigen provoked lymphocytes, and abnormal AKT phosphorylation (Badr et al., 2013).

Thymoquinone (50 mg/kg for 30 days, gastric gavage) decreases blood glucoseby inhibiting the production of gluconeogenic enzymes in the gestational diabetic hamster (Fararh et al., 2005). Furthermore, TQ (80 mg/kg, gastric gavage) ameliorated the glycaemic effects of STZ plus nicotinamide in rats. It increases insulin levels by increasing glucose utilization and

decreasingplasma glucose level causing decrease in hepatic production. It reduces the activities of the enzyme glucose-6-phosphatase and fructose-1, 6-bisphosphatase, which have gluconeogenic effects. The action of TQ on lipid peroxidation, tissue antioxidant, and insulin secretion showed the impact in facilitating the decreased level of glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT), GSH, vitamin E and the increased levels of lipid peroxidation in the diabetic rats. These observations suggests that TQ has amelioration effects on β cell action and against increased free radicals via its antioxidant characteristics (Sankaranarayanan and Pari, 2011). Another result indicates that TQ decreased the glucose level and increased pancreatic insulin release in diabetic rats. TQ improved the toxic effects of STZ, such as heterochromatin aggregation, DNA damage, segregated nucleoli, fragmentation and vacuolization of mitochondria by modulating oxidative stress. These findings suggested that TQameliorates diabetes by protecting β-cells from oxidative damage. Therefore, the antioxidant effect of TQ may improve the damaged β-cells caused by hyperglycemia through down-regulation of inflammatory activity and oxidative stress (Abdelmeguid et al., 2010). These scientific findings indicated that TQ might be effective as an antidiabetic agent in traditional medicine; however, the knowledge on the protective effect of TQ is not sufficient, especially on diabetes and needs to be worked out.

Quercetin.

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a potent bioflavonoid widespread in the plant kingdom, commonly present in onion, apple, berries,and many other nuts, seeds, red wine and vegetables,which form an integral part of the human food (Muhkopyadhyay and Prajapati, 2015). It was reported that quercetin has many advantageous effects on human health, including neuroprotective potential, anticancer activity, anti-allergic activity, anti-inflammatory activity, antiviral and anti-apoptotic activity (Aguirre et al., 2011; Davis et al., 2009; Dok-Go et al., 2003; Ishikawa and Kitamura, 2000). It prevents lipid peroxidation, platelet aggregation, cell death and capillary permeability. It can act as an antioxidant against ROS and inhibit xanthine oxidase (Chang et al., 1993). However, low oral bioavailability has restricted the use of quercetin in the pharmaceutical field.Mostly quercetin is present as glycosides in plants that are poorly absorbed. The absorption of quercetin aglycone is estimated to be as high as 65-81% (Walle et al., 2000).

Several studies showed that quercetin is a probable lead with antidiabetic and antihyperglycemic activityconciliated by alteration in glucose cholesterol and triglycerides levels (Srinivasan et al., 2018). Another study showed that quercetin significantly suppresses postprandial hyperglycemia in patients with type 2 diabetes loaded with maltose, mainly attributed to α-glucosidase inhibition (Hussain et al., 2012). In case of diabetic animals who had obtained quercetin experienced lowerplasma glucose levels than the control groupdid not significantly influence insulin levels estimated by the homeostasis model. Animals that were administered with a 0.08% part of quercetin experienced a range of augmentation, showing a surge in plasma adiponectin, HDL-cholesterol, activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) in the hepatic tissues and decrease in total plasma cholesterol (Jeong et al., 2012). Another finding showed that quercetin imparted an advantage on pancreatic tissues subjected to STZ-induced oxidative stress by directly quenching lipid peroxidation and indirectly by increasing endogenous antioxidant production (El-Baky, 2011). The group treated with quercetin showed a marked decrease in elevated blood glucose, insulin resistance, MDA, NO and sorbitol.

Quercetin remarkably attenuates kidney damagevia its antioxidative action. Quercetin therapysuccessfully lowered diabetic proteinuria and polyuria and enhanced serum creatinine and blood urea nitrogen. Creatinine and urea clearance was also remarkably heightened after

administering quercetin in diabetic rats compared to untreated diabetic rats (Anjaneyulu and Chopra, 2004). Quercetin showed improved renal functioning by inhibiting the upregulation of connective tissue growth factor (CTGF) and transforming growth factor-β1 (TGF-β1) in the kidney of diabetic nephropathic rats (Lai et al., 2012). Previous research had already shown that TGF-β1 and CTGF were involved in the pathophysiological mechanism of DN. Results also depicted that animals treated with quercetin reduced their kidney and body weight ratio.

Another study indicates the potential outcome of quercetin on diabetes-induced mental ailment (Bhutada et al., 2010). Treatment with quercetin (5-20 mg/kg) in STZ-induced diabetic animalsarrested the switch in blood glucose, body weight and presentation in Morris water and elevated plus-maze tasks. In other experiments, quercetin treatment (40 mg/kg) markedly lowered escape inactivity and high time spent in the target quadrant during the Morris water maze task. Kanter and workers (2012) designed a study to show the potential of quercetin on bone minerals, biochemical behaviour and structure in STZ-induced diabetic rats. Quercetin treatment was found to cause elevation in insulin, calcium, and magnesium amount and decreased blood glucose level. Abdelmoaty and workers (2010) performed confirmatory research on quercetin's antioxidant and antidiabetic effects in animal models. The finding suggests that there is no any adverse effect of quercetin on blood plasma glucose level of stock animals.

Moreover, pre-treatment with quercetinprevented diabetes induced by intraperitoneal injection of STZ treated rats. Quercetin increased the antioxidant enzyme activities in STZ-treated rats. Quercetin adequately attenuates cytotoxicity induced due to STZ in renal tissue (Gomes et al., 2014). Quercetin therapy caused a depletion in polyuria and glycemia and eradicated hypertriglyceridemia. In case of renal function activity, quercetin was found to be lowering the proteinuria however, increase plasma levels of uric acid, urea, and creatinine. It also showed beneficial effects on kidney structural changes and decreased oxidative stress and apoptosis in diabetic mice.Quercetin reduces thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats (Anjaneyulu and Chopra, 2004).Quercetin also has beneficial effects on cardiovascular diseases. It enhanced vascular responsiveness in blood vessels of diabetic rats, and these effects were umpired by its antioxidant protection of endothelium-derived nitric oxide (Ajay et al., 2006).Thus, quercetin may be considered in controlling diabetes mellitus and can be used as therapeuticsin diabetic complications.

Curcumin.

Curcumin is an active and essential component of spice turmeric.It is obtained from the rhizomes of a plant which belongs to the ginger family,Curcuma longa. Curcumin is chemically represented as 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione ($C_{21}H_{20}O_6$), which isprimarilypresent in its keto form in both low as well as neutral pH environments and exists in the solid phase. Its solubility in water is markedly reduced at acidic and neutral pH because of its chemical structure. However, it is readily soluble in organic solvents like methyl and ethyl alcohols, dimethyl sulfoxide (DMSO) and acetone (Goel et al., 2008; Aggarwal et al., 2003).

Previous reports have implicated that after oral administration in animals, curcumin undergoes metabolism and produces small metabolites, each having beneficial antioxidant properties. The antioxidant and physicochemical properties of curcumin are governed by the keto-enol-enolate equilibrium of its heptadienone group. Since the electron transfer stabilizes phenoxy radicals, curcumin's free radicals scavenging potential significantly increased. The stabilized radicals may lose the second hydrogen atom from the OH group of the second phenolic, producing a diradical,

which is further converted into quinones, a stable product or cleaved to smaller phenols like ferulic acid.

Like many other phytochemicals, curcumin is also reported to facilitate inflammatory responses. Curcumin regulates TNF-α gene expression by inhibiting specific acetyltransferase p300/CREB, which guides the suppression of histone/nonhistone proteins acetylation and,finally, suppression of transcription (Gupta et al., 2014; Balasubramanyam et al., 2004). Curcumin also regulates TNF-α expression by changing the pattern of methylation of the TNF-α promoter (Reuter et al., 2011). The antioxidant and anti-inflammatory potential of curcumin is considered a promising curative option for diabetes. Initially, it was reported as a hypoglycaemic agent and recently has been noticed as a potent lead in experimental diabetes as well as in different complications. Oral administration of curcumin has been manifested to prevent body weight loss and reduce levels of glucose,glycosylated haemoglobin (HbA1C) and haemoglobin (Hb) and in the blood of streptozotocin as well as alloxan induced diabetic rat models (Zhang et al., 2013; Arun and Nalini, 2002). Ithas also enhanced insulin sensitivity (Murugan and Pari, 2007). Dietary curcumin (0.5% in diet), in the case of the STZ-induced diabetic rat model, effectively lowers the elevated levels of fasting blood sugar, urine sugar, and urine volume (Chougala et al., 2012). A similar study in diabetic mice has investigated the antidiabetic potential of curcumin. The Intraperitoneal route of administration of curcumin has notably altered glucose intolerance, hyperglycemia and hyperinsulinemia in the STZ-induced diabetic mouse model (El-Azab et al., 2011). While in the case of the oral route of administration, it has been proved to lower glucose intolerance in high-fat diet (HFD)-induced obese and insulin-resistant mice (He et al., 2012). Curcumin can potentially regulate the functioning of numerous molecules involved in cell signalling. It lowers the level of a class of transcription factors (such as TNF-a) (El-Azab et al. 2011) and plasma-free fatty acids (El-Moselhy et al., 2011). Curcumin also inhibits the activity of lysosomal enzymes (Chougala et al., 2012), activation of nuclear factor-kappa B (NF-κβ) (Soetikno et al., 2011), protein carbonyl content (Suryanarayana et al., 2007), and lipid peroxidation (El-Azab et al., 2011). It can also lessen the thiobarbituric acid reactive substances (TBARS) and the activity of sorbitol dehydrogenase (SDH) (Murugan and Pari, 2007; Arun and Nalini, 2002). Moreover, It can activate enzymes for glycolysis, gluconeogenic, and lipid metabolic processes in liver (Seo et al., 2008), as well as the nuclear factor, erythroid-2-related factor-2 (Nrf2) function (He et al., 2012). Besides, when complemented with vitamin C and yoghurt, curcumin effectively lowers blood glucose levels, haemoglobin (Hb) and HbA1c in STZ-induced diabeticrats (Gutierres et al., 2012).

Curcumin has been implicated in inhibiting the activation of poly-ADP-ribose polymerase-1 and neutralizing cytokines (TNF-α, IL-1b, etc.), causing NF-kB translocation leading to islets viability and diminishing the reactive oxygen species (ROS) production level. Its therapy enhances small pancreatic islets number and reduces the infiltration of lymphocytes in the pancreatic islets (Chanpoo et al., 2010). In the db/db mice model, curcumin increases the AMPK and PPARγexpression and reduces NF-κβ protein levels, whereas no change in the PGC-1α or SIRT1 expression has been observed. Consequently, curcumin is effective for treating diabetic complications by regulating the expression of PPARγ,AMPK and NF-κβ (Jimenez-Flores et al., 2014).

Tocotrienol.

Vitamin E supplementation has a crucial role in slowing the onset of diabetic complications andretarding the progression of complications (Jain et al., 2012). Tocopherol and tocotrienolare the two significant constituents of vitamin E (Tan et al., 2018). Structurally, vitamin E contains eight chemically different molecules: α-, β-, γ-, δ-tocopherols having long phytyl tails and α-, β-, γ-,δ-

tocotrienol having short farnesyl tails (Shen et al., 2018; Wong et al., 2017). Tocotrienol isthe primary form of vitamin E in cereal grains and vegetables such as wheat, rice, barley and annatto. Out of these two, tocotrienol is considered the most potent antioxidant than α-tocopherol (Serbinova et al., 1994). They have better anti-glycemic, anti-cholesterolemic, anti-inflammatory, neuroprotective and cardioprotective properties (Peh et al., 2016). Tissues having layers of saturated fatty acids like liver and brain penetrated more effectively with the unsaturated side chain of tocotrienol (Suzuki et al., 1993).

Studies have shown that a daily supplement of (200 mg/kg) tocotrienol rich fraction (TRF) reduces the extent of oxidative stress markers by limitinglipid peroxidation and enhancing antioxidant status in streptozotocin (STZ) induced diabetic animals (Matough et al., 2014). It effectively prevents the increase in AGE formation, a toxic byproduct of glucose, protein, or lipid oxidation and decreases serum glucose and glycated haemoglobin in diabetic rats (Nazaimoon and Khalid, 2002). Another study indicates *in vitro* antioxidant effect of tocotrienol on erythrocytes and LDL inpeople with type 2 diabetes against oxidative damage (Iqbal et al., 2012). Tocotrienols extracted from annatto have been proven beneficial in maintaining bone matrix and improving glucose homeostasis in type 2 diabetic mice by lowering the inflammatory response (Shen et al., 2018). Another study has revealed that activation of the NF-κβ signalling pathway is linked with diabetes-induceddisabilities and directs towards the therapeutic potential of tocotrienol in diabetic encephalopathy (Kuhad et al., 2009). Rats with STZ-induced diabetes mellitus are treated with oral tocotrienols, which notablyamelioratedbehavioural, biochemical and molecular alterationslinked with diabetes viablocking of the NF-κβ signalling cascadefor ten weeks. Furthermore,combinational therapy of insulin-tocotrienol has a more substantial effect on molecular markers than sole therapy in diabetic rats. Another study reveals that TRF significantly reduces dyslipidemia and inhibits the development of chronic renal dysfunction in rats caused by atherogenic factors (Khan et al., 2015). Tocotrienol from palm oil reduces serum creatinine in patients with type 2 diabetes mellitus, and serum Nε-CML is a potent biomarker for diabetic nephropathy (Tan et al., 2018). It suggests that tocotrienol couldbe advantageous for the current therapy of diabetic neuropathy.

A separate investigation has shown that tocotrienol therapy in treating chronic diabetic rats causes a decline in blood glucose level and HbA1 nearexpected values against diabetic dyslipidemia in rats (Ali et al., 2015). These results suggest a unique relationship between glycemic control and tocotrienol therapy. More clinical and preclinical studies are required to realize the beneficial effect of tocotrienol and its potential against diabetic complications.

Ferulic acid.

Ferulic acidis derived from cinnamic acid obtained from rice, wheat, barley, orange, coffee, apple, peanuts, etc.,produced bythe metabolism of phenylalanine and tyrosine. Ferulic acid is an antioxidant, helps in scavenging free radicals, preventing lipid peroxidation, and apoptotic cell death (Fetoni et al., 2010), and hinders thesecondary free radicals toxicity produced by carbon tetrachloride(CCl_4) (Srinivasan et al., 2005).Downregulating NOS protects cells from reactive nitrogen species (RNS) (Koh, 2012).

Ferulic acid and 5-O-feruloyl-L-arabinofuranose are transported to the intestine escaping from degradation by stomach acid after ingestion (Zhao and Moghadasian, 2008). In the colon, linked ferulic acid is delivered from sourcesubstances by microbial enzymes cinnamoyl esterase, xylanase, and ferulic acid esterase and is primarilyingest by passive diffusion (90%), while a trace amount via active transport through monocarboxylic acid transporter (Poquet et al., 2008; Couteau et al., 2001).

Intraperitoneal administration of ferulic acid to the animals has excreted a major urinary metabolite as 3-hydroxy phenyl propionic acid (Booth et al., 1959).

Ferulic acid has beneficial therapeutic potential in treating diabetes by acting at different levels. Ferulic acid (10-50 mg/kg per os) has depicted antioxidant activity, inhibited lipid peroxidation markers, increased the cell stress response and lowered NF-κβ immunoreactivity in different body tissues samples and serum of alloxan as well as STZ induced diabetic animals (Roy et al., 2013; Ramar et al., 2012). Ferulic acid administration (10 and 40 mg/kg per os) for three weeks successfully lowered blood glucose levels in STZ induced diabetic rats (Prabhakar et al., 2013). Results from another researcher confirmed that oral administration of ferulic acid for 17 days causes reduced blood glucose levels as well as improved plasma insulin in the db/db mice model. Further, it has been confirmed that ferulic acid helps in the synthesis of enzyme glycogen from the liver and glucokinase leads to regulating the blood glucose level (Jung et al., 2007) and acts as an α-glucosidase inhibitorby inhibitingenzymes maltase and sucrase in rats (Adisakwattana et al., 2009).

Ferulic acid eliminates the cytokine expression transforming growth factor-b1 and oxidative stress markers, decreasing thickness of glomerular basement membrane, volume of glomerular and expansion of mesangial matrix (Choi et al., 2011; Fujita et al., 2008). Current study reported thata 6-week therapy of ferulic acid (20 mg/kg per os) could inhibit enzyme aldose reductase in streptozotocin-treated animals. The reduced inhibitory effect of diabetic hypertension may be caused due to various mechanisms, includingpreventing inflammation and ROS production and enhancing NO formation and vascular ability to contract (Badawy et al., 2013). Ferulic acid (10-40 mg/kg per os) therapy along with the coadministration of metformin and thiazolidinedione potentiated the hypoglycaemic actionin streptozotocin-induced diabetic rats. The synergistic potential of ferulic acid along with metformin or thiazolidinedione improved the lipid profile in diabetic animals, and remarkably, reducedmajor adverse effects when co-administered with thiazolidinedione (Prabhakar et al., 2013).

Naringin.

Naringin (chemically known as 4,5,7-trihydroxyflavanone-7-rhamnoglucoside) is a bioflavonoid isolated from tomatoes, grapefruit, and related citrus fruits. The aglycone portion of Naringin (naringenin) contains two rhamnose units at its 7^{th} carbon. Recently, researchers showed much interest in the efficacy of citrus fruits due to their intake linked with a reduced risk of some debilitating chronic diseases and hence increased survival (Chen et al., 2002).

Studies have shown that naringin has potent antihyperglycemic, antidyslipidemic capability and cardiac function ameliorating action in high-fat diet (HFD)/streptozotocin (STZ) -induced type 2 diabetic rats (Al-kurdy, 2014; Ahmed et al., 2012). The result indicates that naringin therapy potentially improved the increasedglucose levels, glycated haemoglobin, AST, LDH, and CK-MB and lessened the insulin content in serum and glycogen content of hepatic and muscle insulin-resistant diabetic rats. It was able to reduce lipid profile and serum adiponectin and resistin levels. Naringin exhibits an antidiabetic effect by upregulating adipose tissue PPARγ and adiponectin expression and reducing resistin expression. Another study also established that not onlyglucose and glycosylated haemoglobin levels were remarkablyreduced,butan increase in insulin levelsin serum was also observed in diabetic rats treated with naringin (Mahmoud et al., 2013).Naringin plays a vital role in arresting hyperglycemia, partly by mediating the increase in hepatic glycolysis and glycogen concentration and/or lowering hepatic gluconeogenesis in C57BL/KsJ-db/db mice. Naringin treatment reduces the activity of hepatic glucose-6-phosphatase and phosphoenolpyruvate

carboxykinase and increases the activity of hepatic glucokinase in diabetic rats (Pari et al., 2010; Jung et al., 2004). Another study proves that Naringin ameliorates insulin resistance, dysfunction in β-cell, hepatic steatosis, and kidney damage by regulating oxidative stress, inflammation, and dysregulated adipocytokines generation, up-regulation of PPARγ, heat shock protein-27 and heat shock protein-72 in type 2 diabetic rats (Sharma et al.,2011).

Naringin significantly improvesthe hypoglycemic and antioxidative activity in STZ induced diabetic rats. There was a depletion in glucose level and TBARS level and an increment in serum insulin concentration and antioxidative enzyme activities in diabetic rats treated with naringin (CAT, SOD, GPx, PON) (Mamdouh and Abd, 2004). Naringin protects pancreatic β-cells against oxidative stress-induced apoptosis by limiting both intrinsic (mitochondria-mediated) and extrinsic (death receptor-mediated) pathways(Lim et al., 2018). The result showed that the protective properties were linked with suppressing DNA damage response, nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK) mediated signalling pathways, and reducing ROS accumulation proinflammatory cytokine production in the pancreas.

Another investigation showed that Naringin attenuates hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in HFD/STZ induced type 2 diabetic rats. The results showed that glucose levels, glycosylated haemoglobin, MDA, TNF-α, NO, and IL-6 were significantly decreased in diabetic rats on the administration of Naringin (Mahmoud et al., 2012).Naringin reduced diabetic retinopathy by inhibiting proinflammatory cytokines, tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), oxidative stress, and NF-κB inactivation *in vivo* and *in vitro* in experimental models of diabetic retinopathy (Liu et al., 2017). It ameliorates cognitive deficits by lowering the oxidative stress and proinflammatory factors, caspase-3 and caspase-9 and activating the PPARγ signalling pathway in a type 2 diabetic rat model (Qi et al., 2015).

Naringin reduces myocardial damage by inhibiting the inflammatory reactions mediated by NF-κB and retards the progression of diabetic cardiopathy (Wu et al., 2013). Naringin also protects against high glucose-induced human endothelial cell injury through its antioxidant properties by downregulating CX3CL1 protein and improving mitochondrial function (Li et al., 2017).Naringin decreases malondialdehyde level, the marker of lipid peroxidation, reduction in protein glycation, and activates GSH synthesis in L6 myoblast cell (Dhanya et al., 2015).

Conclusion

T2DM is a fast-growing metabolic disorderworldwide,posing a significant burden on health resources. The existing drugs have been identified with many adverse effects. There is an urgent need for better treatment for people affected by diabetes. Natural products can be an alternative for the treatment of diabetes without any adverse effects. Therefore more researchis needed to explore the potential of natural products as a source of the drug.This paper highlights the antidiabetic effects of some of the natural products for the management of diabetes and its associated complications.

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