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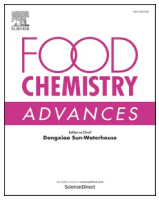

Role of dietary antioxidants in diabetes: An overview

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ABSTRACT

Diabetes mellitus (DM) is a devastating medical condition which has become one of the top ten causes of most deaths, with a 70 % increase since 2000. DM is characterised by elevated plasma glucose levels. The excess glucose levels have been found to have a causal link with the development of reactive oxygen species leading to oxidative stress. Failure of the body's intracellular antioxidant system to compensate for increased oxidative stress results in the activation of stress-sensitive intracellular signalling pathways and ultimately cellular damage, which leads to the pathogenesis of DM. It is evident that naturally occurring dietary antioxidants such as vitamins E, A, and C, plant polyphenols, carotenoids, flavonoids, glutathione, alpha-lipoic acid, and polyamines all provide significant protection against diabetes. According to research, antioxidant therapy protects the beta-cell against oxidative stress-induced apoptosis, preserves beta-cell function, and reduces diabetic-related complications. As a result, the use of naturally occurring antioxidants has increased dramatically, not only because of their natural therapeutic effects, but also because of the safety concerns associated with synthetic antioxidants, as well as their affordability and availability. This paper compiled the current research on the role of oxidative stress in diabetes and the significance of natural dietary antioxidants in mitigating that effect.

Introduction

Diabetes mellitus (DM) is a heterogeneous disorder with multiple aetiologies associated with disruptions in carbohydrate, lipid, and protein metabolism, resulting in long-term complications (Antar et al., 2023). Hyperglycemia, or high plasma glucose levels, is a defining feature of this condition and is responsible for organ dysfunction in areas such as the heart, kidneys, nerves, and eyes (Tsalamandris et al., 2019). According to the International Diabetes Federation, approximately 537 million adults aged 20 to 79 have DM, with that figure expected to rise to 783 million by 2045 (IDF Diabetes Atlas, Tenth Edition, n.d., 2021).

The American Diabetes Association introduced the new classification of DM (type 1 and type 2 DM) in place of the terms insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus, which were previously recommended by the WHO based on the clinical description of the patient (Eiselein et al., 2004). Type 1 diabetes (T1DM) affects 5–10 % of people with DM and appears at a younger age (juvenile-onset diabetes) due to a failure of the pancreas to produce insulin as a result of cellular-mediated autoimmune destruction of insulin-producing cells. Type 2 diabetes (T2DM), which affects 90–95 % of people with DM, develops later in life as a result of insulin resistance and insufficient insulin production (Ruze et al., 2023). T2DM is caused by a combination of genetic and environmental factors. According to a study conducted by Tillil and Köbberling (1987), when a single parent has T2DM, offspring are at 40 % risk of developing the condition, and the risk increases to 70 % if both parents have T2DM. Although genetic factors contribute to insulin resistance, diet and lifestyle factors such as obesity, sedentary lifestyle, ageing, consumption of energy-dense foods, and physical inactivity are important predictors of T2DM (Ruze et al., 2023).

T1DM and T2DM being the main subtypes of DM, there are other subtypes of DM, namely, gestational DM and specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

Several research studies have shown that diabetic patients have low levels of plasma antioxidants (Pieme et al., 2017; Tiwari et al., 2013), and thus the failure of the body's innate antioxidant scavenging system to neutralise free radicals causes oxidative stress and, ultimately,

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Footnote abbreviations

DM	diabetes mellitus
T2DM	type 2 diabetes mellitus
ROS	reactive oxygen species
RNS	reactive nitrogen species
RSS	reactive sulphur species
SOD	superoxide dismutase
GPX	glutathione peroxidase
GSH	glutathione
AGE	advance glycated end product
PKC	protein kinase C
NADPH	nicotinamide adenine dinucleotide phosphate
UDP-GlcNAc	uridine diphosphate-NAcetylglucosamine
GFAT	glucosamine-fructose amidotransferase
HBP	hexosamine biosynthesis pathway
DNA	deoxyribonucleic acid
GPX4	glutathione peroxidase 4
ALA	alpha-lipoic acid
LA	lipoic acid
PAs	polyamines
HbA1c	glycosylated haemoglobin

cellular damage. These findings suggest that it is vital to supplement the imbalance with naturally occurring antioxidants. This review discusses the causes of oxidative stress in DM and the role of naturally occurring antioxidants in DM management.

Free radicals and their role in diabetes mellitus

Free radicals are reactive chemical species that are formed in the human body due to exposure to various physiological and pathological conditions as well as to external sources (Yashin et al., 2017; Zhu et al., 2023). Generally, reactive molecules are derived from oxygen, nitrogen, and sulphur and are generated in the cell membrane, mitochondria, nucleus, lysosome, peroxisome, endoplasmic reticulum, and cytoplasm. Reactive Oxygen Species (ROS), reactive nitrogen species (RNS), and reactive sulphur species (RSS) can be classified as radicals and non-radicals. Radicals contain a minimum of one electron in the valence shell or outer orbit, where as non-radicals have no unpaired electrons. Because of the presence of unpaired electrons, free radicals are capable of accepting or donating electrons; thus, they exhibit an unstable nature (Zhu et al., 2023).

At lower concentrations, free radicals also carry out certain important physiological functions in the human body, such as helping to kill pathogenic organisms during the phagocytic process, carrying out cell signalling pathways, apoptosis, ion transportation, gene regulation and expression, and controlling the vascular tone and blood pressure (Zhu et al., 2023).

However, higher free radical concentrations, combined with insufficient function of the intracellular antioxidant system, cause the accumulation of high free radical levels in the body, leading to oxidative stress, which is a major cause of a number of noncommunicable human diseases, including DM (Zhu et al., 2023).

Antioxidants

Antioxidants are important chemical compounds known for a variety of beneficial functions, including neutralising or scavenging free radicals, reducing oxidative stress, protecting against oxidative degeneration in the body, and controlling rancidity formation, preventing the formation of toxic oxidation products, maintaining nutritional quality, and extending shelf-life in food systems (Yashin et al., 2017).

Antioxidants are classified into groups based on their nature and properties. Antioxidants are categorised as enzymatic or non-enzymatic based on their scavenging mechanism. Enzymatic antioxidants break down oxidative products into hydrogen peroxide and water in the presence of cofactors, whereas non-enzymatic antioxidants function by interrupting the free radical chain reaction. Antioxidants can also be classified according to their solubility, size, and natural occurrence (Aziz et al., 2019; Flieger et al., 2021). Table 1 contains detailed information on antioxidant classification.

Oxidative stress and diabetes mellitus

Oxidative stress is caused by an imbalance between the free radicals of ROS, RNS, and RSS and the antioxidant defence system, which is involved in the pathogenesis and aetiology of a variety of diseases, including diabetes, cardiovascular disease, neurodegenerative disorders, cancer, and other inflammatory diseases (Jomová et al., 2023). In DM, oxidative stress is perpetuated by the production of free radicals and the suppression of the existing antioxidant system (Caturano et al., 2023). $\bullet O_2^-$ is produced by cells in regular energy production mechanisms, and this is neutralised by the innate oxidative system. High glucose levels, on the other hand, induce changes in mitochondria, increase oxidative phosphorylation, and result in increased free radical production in conditions such as DM (Caturano et al., 2023). Furthermore, ROS in DM is produced by a variety of mechanisms, including an activated polyol pathway, increased formation of advanced glycated end products (AGEs), stimulation of the AGE receptor, activation of protein kinase C (PKC), and hexosamine pathway overactivity (Caturano et al., 2023).

Polyol pathway

Increased glucose levels in DM can result in more than 30 % of glucose being transported to the polyol pathway, where it is reduced to sorbitol and then oxidised to fructose (Caturano et al., 2023). Aldose reductase catalyses the reduction of glucose to sorbitol, and NAD+-dependent sorbitol dehydrogenase catalyses the oxidation of sorbitol to fructose. Aldose reductase consumes nicotinamide adenine Dinucleotide Phosphorate (NADPH) as a cofactor for activity, resulting in NADPH depletion, which is a critical molecule in the regeneration of reduced GSH. Oxidative stress is caused by a low level of reduced GSH.

Table 1
Classification of antioxidants.

Type of classification	Sub classification	Examples of antioxidants
Based on activity	Enzymatic	Superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase
	Nonenzymatic	Vitamin C, vitamin E, plant polyphenol, carotenoids, and glutathione (GSH)
Based on solubility	Water-soluble	Vitamin C
	Lipid soluble	Vitamin E
According to size	Small molecule	Vitamin C, vitamin E, carotenoids, and GSH
	Large molecule	enzymes (SOD, catalase, and GPX) and sacrificial proteins (albumin)
Based on occurrence	Natural Antioxidant minerals:	Selenium, copper, iron, zinc, and manganese.
	Antioxidant vitamins:	Vitamin C, E, and B.
	Phytochemicals:	flavonoids, catechins, carotenoids, carotene, lycopene, and herbs and spices such as diterpene, rosmariquinone, thyme, nutmeg, clove, black pepper, ginger, garlic, curcumin, and derivatives.
	Synthetic	Butylated hydroxyl anisole, butylated hydroxytoluene, propyl gallate, metal chelating agent, tertiary butyl hydroquinone, and nordihydroguaiaretic acid.

Sources: (Aziz et al., 2019; Flieger et al., 2021).

Furthermore, decreased NADPH levels cause an increase in NADH, which produces more ROS (Caturano et al., 2023).

Advance glycated end product (AGE) formation and age receptors

AGEs are formed intracellularly through a complex reaction. In hyperglycaemia, glucose reacts with proteins to form Schiff bases, which will then turn into AGEs (Caturano et al., 2023). The formed AGEs and precursors are capable of modifying the external environment and resulting in miscommunication between cells and the environment. Cell damage through cross-linking with proteins and altering the circulating proteins leads to oxidative stress by activating cell signalling and gene expression (Caturano et al., 2023).

Activation of protein kinase C (PKC) enzyme

PKC is an enzyme that is activated by a co-factor synthesised at a high level of glucose concentration in the blood. Thus, activated PKC activates NADPH oxidase and produces ROS. Activation of NADPH is also known to cause damage to the renal and retinal systems and lead to diabetic nephropathy and retinopathy, respectively. PKC also affects nitric oxide, which ultimately results in vasoconstriction (Caturano et al., 2023).

Overactivity of the hexosamine pathway

The hexosamine biosynthesis pathway (HBP) involves 2–5 % glucose metabolism, in which the glycolysis intermediate fructose-6-phosphate is converted into glucose-6-phosphate and then to Uridine diphosphate-NAcetylglucosamine (UDP-GlcNAc). The conversion of fructose-6-phosphate to glucose-6-phosphate is carried out by the rate-limiting glucosamine-fructose aminotransferase (GFAT) enzyme, and the conversion of glucose-6-phosphate to UDP-GlcNAc by UDP-NAcetylglucosamine synthase (Schleicher & Weigert, 2000). Thus, UDP-GlcNAc is a vital molecule in protein and lipid glycosylation and in the post-translational modification of proteins. Under hyperglycaemic levels, the activity of GFAT and UDP-NAcetylglucosamine synthase is upregulated due to the excessive entry of fructose-6-phosphate into HBP. Thus, the hyperactivity of the enzyme and HBP is known to cause alterations in gene expression, increased expression of transcription factors, and ultimately is responsible for the pro-oxidative role leading to oxidative stress (Edwards et al., 2008).

The produced ROS in all these mechanisms are known to cause oxidative stress and lead to protein oxidation, lipid peroxidation, DNA damage, reduced antioxidant levels, insulin resistance, impaired insulin secretion, and glucose utilisation (Oguntibeju, 2019). Butkowski and Jelinek (2017) conducted a study among diabetes and non-diabetes subjects to understand the effect of oxidative stress in T2DM and showed the increased levels of glycosylated haemoglobin (HbA1c), which causes the oxidative stress, and also the relationship of hyperglycaemia and oxidative stress. Further, several studies have shared evidence for the relationship between oxidative stress, which results in increased production of ROS in DM, and the pathogenesis and progression of diabetic nephropathy (Hojs et al., 2020; Sagoo & Gnudi, 2018), diabetic retinopathy (Haydinger et al., 2023; Kang & Yang, 2020), and diabetic neuropathy (Chun & Park, 2020; Pang et al., 2020).

Dietary antioxidants and diabetes mellitus

Naturally occurring antioxidants are phytochemicals or vitamins with low or high molecular weight that are synthesised by plants. Vitamins E, A, C, carotenoids, flavonoids, plant polyphenols, GSH, uric acid, alpha-lipoic acid (ALA), curcumin, polyamines (PAs), and melatonin are all naturally occurring antioxidants (Table 2). Epidemiological studies have found a strong link between dietary antioxidant intake and protection against DM. Previous research indicates that antioxidant therapy protects the beta-cell against oxidative stress-induced apoptosis and preserves beta-cell function, and antioxidants reduce diabetic-related complications (Kanwugu et al., 2021).

Table 2
Dietary antioxidants and sources.

Naturally occurring antioxidants	**Sources**
Vitamin E	Wheatgerm oil, Sunflower oil, Almonds, Safflower oil, Hazelnuts, Peanut butter, Corn oil, Spinach, Broccoli, Soybean oil, Kiwifruit, Mango, Tomato Milk, Egg (Rizvi et al., 2014)
Vitamin C	citrus fruits (Orange, lemon), kiwi, mango, broccoli, tomatoes, and peppers, blueberries, strawberries, grape (Lykkesfeldt et al., 2014)
Vitamin A	Animal Source -Liver, egg yolk (not the white) milk (including human breast milk), cheese and butter. Plant sources - mangos, papaya, many of the squashes, carrots, sweet potatoes and maize Other sources - red palm oil and buriti palm oil (Gilbert, 2013)
Carotenoids	kale, spinach, broccoli, marigold flower, egg yolks (Bernstein et al., 2016) beta carotene - buriti (*Mauritia vinifera* Mart.), tucumã (*Acrocomia mokayáyba* Barb. Rodr.), bocaiúva, acerola, mango, pumpkin, carrot, nuts, camu-camu (*Myrciaria dubia*), rose hip fruits lycopene - tomato, cherry, guava, and guava, watermelon, Thai papaya (Mezzomo & Ferreira, 2016)
Flavonoids	Onions, kale, lettuce, tomatoes, apples, grapes and berries Green tea, grape seeds, red pepper, apple, citrus fruits, berries, peaches (Panche et al., 2016)
α Lipoic acid	Red meat, spinach, broccoli, tomato, garden pea, Orange, yeast, broccoli, potatoes, carrots (Wollin & Jones, 2003).
Polyphenol	Tea especially green and red tea. Potatoes, wheat, apricot and tomatoes Fruits such as berries, peaches and almonds (Anwar et al., 2018)
Glutathione	Asparagus, avocado, cabbage, Brussels, sprouts, spinach, garlic, cucumber, almonds (Anwar et al., 2018)
Polyamines	Cereals, legumes, wheat germs, soybeans, mushrooms, cauliflower, spinach (Larqué et al., 2007)

Vitamin E

Vitamin E is a lipid-soluble, odourless, yellow to amber, small antioxidant molecule having a chromanol ring with a hydrophilic side chain located at the C2 position (Fig. 1). Vitamin E comprises four tocopherols and four tocotrienols of α-, β-, γ-, and δ- compounds. Based on the number and position of methyl groups, there are eight compounds that comprise vitamin E (Niki & Abe, 2019). The structural difference between tocotrienols and tocopherols is that the isoprenyl side chain present in tocotrienols is unsaturated, whereas the phytyl side chain present in tocopherol is saturated. Even though α-tocopherol is the active and main form in humans, tocotrienols are found to have a higher antioxidant capacity than α-tocopherol (Szewczyk et al., 2021).

Vitamin E cannot be synthesised by the human body, and its biosynthesis is limited to photosynthetic plants and organisms

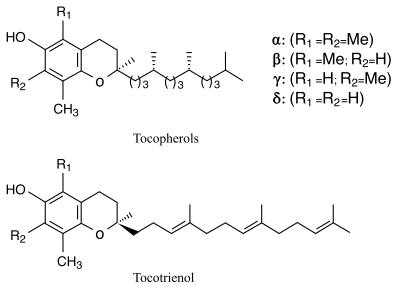


Fig. 1. Vitamin E.

(Muthulakshmi et al., 2023). It is one of the major antioxidants that exhibits scavenging properties in vitro and in vivo and thus protects from oxidative stress and several medical conditions. Additionally, vitamin E is also known for its role in cell signalling, structural balance through membrane stabilisation, enzyme regulation, immune function, and nerve function (Lewis et al., 2018).

Due to the increased free radicals in the body, the level of antioxidant enzymes decreases. In a study conducted by Baragob et al. (2014), administration of 440 mg/kg (body weight) of vitamin E once a week for 1 month showed an increased level of SOD and GPX activity. In biological membranes, lipid-hydroperoxide is effectively reduced by glutathione peroxidase 4 (GPX4), and cells that lack GPX4 showed protection from unwanted apoptosis by vitamin E (X. Jiang et al., 2021).

Vitamin E supplementation studies show cellular protection by decreasing lipid peroxidation, protein oxidation, protein glycation, and cytotoxicity (Devaraj et al., 2008; Seven et al., 2004). This is further evident in a study conducted by Ihara et al. (2000), which showed that vitamin E inhibits the oxidative stress sequence. Further, a study conducted by Wang et al. (2010) among Chinese women with metabolic syndrome showed that supplementation with vitamin E decreased total cholesterol and indicators of oxidative stress.

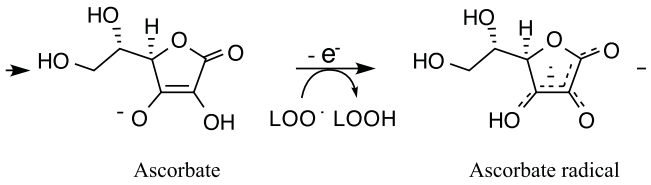
In the context of DM, vitamin E improves glucose metabolism (Asbaghi et al., 2023), defends the cell against oxidative damage, contributes to minimising the hyperglycaemia induced vascular complications, improves beta cell function, and improves insulin action (Koya, Lee et al., 1997). Increased antioxidant (especially vitamin E) levels have been positively correlated with decreased plasma glucose levels by increasing glucose metabolism (Shamsi et al., 2004). Further, a randomised controlled study conducted among individuals with prediabetes to evaluate the effects of delta-tocotrienol supplementation showed a significant improvement in glycaemic control parameters (Suleman et al., 2022).

Furthermore, vitamin E supplementation in diabetic-induced rats reduced urinary protein (Montero et al., 2000), basement membrane thickening in the retina (Yülek et al., 2007), lipid oxidation marker F2-isoprostanes (Dav et al., 1999), diabetic retinopathy, and microvascular and macrovascular complications (Rahimi-Madiseh et al., 2016). A vitamin E supplementation study also found reduced oxidative stress in the glomeruli and reversal of renal dysfunction in DM-induced rats (Chopra et al., 2014). In another study, vitamin E supplementation improved retinal blood flow in patients with short-term diabetes and little retinopathy (Bursell et al., 1999).

However, a few studies found no improvement in patients with DM who were given vitamin E supplements (Choi et al., 2004; Gokkusu et al., 2001). This could be due to a variety of factors such as supplementation dose, time period, participant's diabetic history, compliance, use of antioxidants alone or in combination with other drugs, and so on. This was demonstrated in a study conducted by De Oliveira et al. (2011), who found that supplementing with vitamin E did not improve DM complications in patients with a long history of diabetes. Furthermore, Asbaghi et al. (2023), Suksomboon et al. (2011), and others summarised the effect of different doses of vitamin E supplementation on glycemic control and insulin resistance in diabetic patients in a systematic review and meta-analysis.

Vitamin-C

Vitamin C/ascorbic acid is an important organic compound that has six asymmetrical carbon atoms ($C_6H_8O_6$) and is structurally similar to glucose. Vitamin C carries out redox reactions in the biological system as it exists in ascorbate (reduced) and dehydroascorbic acid (oxidised) forms and is capable of being easily converted (Fig. 2). Vitamin C naturally occurs in many foods, and it is a water-soluble week acid. It is a white solid that is capable of being destroyed by alkali, light, humidity, heavy metals, etc. Even though vitamin C is biosynthesised in many plants and animals by oxidation of glucose, galactose, and mannose



Ascorbate Ascorbate radical

Fig. 2. Reduction mechanism of ascorbic acid.

through the uronic acid pathway, it is not biosynthesised in many primates (including humans) due to a mutation in the genes responsible for the production of the gulonolactone oxidase enzyme (Fujii, 2021). Ascorbic acid has various functions, such as free radical scavenging, antioxidant activity, cholesterol level reduction by converting it to bile acids, increased iron absorption, amino acid metabolism, acting as an enzyme cofactor, etc. Further ascorbic acid deficiency will also result in a condition known as scurvy, a lethal condition unless properly treated. Thus, vitamin C is a true vitamin and is used for the treatment of a range of conditions (Chambial et al., 2013).

Vitamin C donates electrons from the double bond between the second and third carbons to free radicals present in the body and results in ascoryl radicals, which are less reactive and stable than the other radicals due to resonance stabilisation (Afkhami-Ardekani & Shojaoddiny-Ardekani, 2007). Thus, the chemical nature of vitamin C helps in the speedy removal of harmful reactive species and makes it a vital radical scavenger. Vitamin C also takes part in the regeneration of vitamin E from its oxidised state to its active state and prevents the oxidation of biomolecules by donating electrons to various enzymatic and nonenzymatic reactions (Skrzydlewska & Skrzydlewska, 2022). Several studies show supplementation with vitamin C reduces free radicals and biomolecule oxidation (Dakhale et al., 2011; Popovic et al., 2015; Traber & Stevens, 2011). Further, vitamin C is also known to protect from diabetic complications—microvascular and macrovascular dysfunction—by protecting and increasing nitric oxide, which is necessary for vasodilation and endothelial dysfunction (Golbidi et al., 2011; Wollin & Jones, 2003).

Many observational and interventional studies have been conducted to better understand the relationship between vitamin C and DM, and the studies have revealed that vitamin C concentration is low in DM patients (Bansal & Hadimani, 2021; Carr et al., 2022; Will et al., 1999). This is due to competition between glucose and the oxidised form of vitamin C, which are both transported via glucose transporters. Dehydroascorbic acid is inhibited from cellular uptake in DM due to high plasma glucose levels, and thus it is excreted from the body, resulting in decreased levels (Wilson et al., 2017). This problem can be solved by taking in ample amounts of vitamin C. Several studies have shown that vitamin C supplementation improves glycaemic control in DM patients by lowering plasma glucose levels, HbA1c, food intake, and postprandial blood glucose levels (Dakhale et al., 2011; Zhou et al., 2016). The results of studies on the effects of vitamin C supplementation for diabetes management, as well as dose, on human and animal models have been summarised (Ashor et al., 2017; Mason et al., 2023; Nosratabadi et al., 2023).

Vitamin-A

Vitamin A is an unsaturated lipid-soluble organic compound composed of a conjugated polyene linked to a beta-ionone ring consisting of a trans pi bond on itself with three methyl groups. It contains retinol, retinal, retinoic acid, retinyl palmitate, and many provitamin-A carotenoids, according to the attached functional group (Fennema, 2007). Vitamin A cannot be produced by the body and must be obtained through diet. Animal tissues (yellow fat-soluble substances) contain the majority of vitamin A, which is easily absorbed in the small intestine; plant sources do not contain vitamin A. Plants that contain carotenoids,

on the other hand, are converted to retinol in the intestine and thus serve as provitamins. Retinol is stored in the liver after absorption and serves as an immediate precursor for retinal and retinoic acid. Vitamin A is well known for upregulating antioxidant enzymes and antioxidant activity, in addition to its functions in gene regulation, vision, immunity, bone remodelling, and reproduction (D'Ambrosio et al., 2011). Vitamin A eliminates lipid peroxyl radicals (LOO.) by trapping them with an additional reaction to a beta-ionone ring's trans pi bond. The resulting tertiary and highly conjugated trans-retinol carbon radical intermediate is relatively stable due to resonance and not reactive enough to induce further lipid peroxidation under normal conditions. Furthermore, recent research provides evidence for a link between DM and vitamin A levels (Abahusain & N, 2002; Kim et al., 2017; Yamakoshi et al., 2002). A study conducted by Rhee and Plutzky (2012) found that vitamin A has a role in the regulation and development of the pancreas. In an animal study, supplementation with vitamin A exhibited a correlation between vitamin A intake and a reduction in DM-related problems (Meerza et al., 2016). Iqbal and Naseem (2015), in a review article focusing on vitamin A intervention in T2DM patients, concluded the novel pathways highlighting the associations between vitamin A and diabetes pathogenesis. Further detailed information on DM complications and the role of vitamin A is explained in a review article written by Trasino and Gudas (2015) and Y. Zhang, Wang et al. (2021). However, it was noted that more studies are warranted to affirm the effect of vitamin A on DM. Further dose-moderation studies are required to maximise the effect of vitamin A supplementation in patients with DM.

Alpha-lipoic acid

Lipoic acid (LA), or ALA, is a naturally occurring short-chain fatty acid. It is also known as 1,2-dithiolane-3-pentanoic acid or thioctic acid. LA is synthesised enzymatically in plant and animal mitochondria from octanoic acid (a fatty acid) and cysteine (a sulphur-containing amino acid) (Moussa et al., 2019) and is known for oxidative decarboxylation of α-keto acids. ALA fights against cellular injuries triggered by free radicals and reduces oxidative stress. Also, it has the capability to restore antioxidants such as GSH, vitamin E, and vitamin C (Moussa et al., 2019). It is the main cofactor for energy production in the mitochondria and the co-factor for the pyruvate dehydrogenase complex. Also, it contributes to the regulation of carbohydrate and lipid metabolism (Capece et al., 2022).

ALA is capable of scavenging ROS produced during lipid peroxidation and guarding the cell structure against damage. The continued supplementation of LA in diabetic rats was associated with a diminution of both hyperglycaemia and diabetic nephropathy ("Chemistry & Antioxidant Activity of Plants Containing Some Phenolic Compounds.", 2015). In a recent multicenter, randomised, double-blind study, it was observed that neurological functions improved after treatment with ALA for four years in patients with diabetic neuropathy (Ziegler et al., 2011). ALA decreases oxidative stress, which is produced by DM, by increasing the sensitivity of insulin, thereby maintaining glycaemic control and decreasing ROS generated by hyperglycemia and dyslipidaemia. LA is also known to have potential in the preventive or ameliorative effect of pancreatic destruction and insulin resistance in both type I and type II diabetes (Capece et al., 2022). A number of review articles have been published on the safety and efficacy of ALA supplementation in DM (Fogacci et al., 2020; Jibril et al., 2022), the therapeutic effect of ALA in DM (Jeffrey, Samraj & Raj, 2021), and the effect of ALA in the prevention of DM complications (Jeffrey, Samraj & Behin, 2021; Vakali et al., 2022).

Carotenoids

Carotenoids are lipophilic compounds found as colour pigments in a variety of plants, algae, and bacteria. The most prominent carotenoids are lycopene, beta carotene, and xanthophyll. The majority of carotenoids have around 40 carbon atoms in molecules with extended conjugated double bonds. Carotenoids are classified into two groups based on their composition and functional groups, such as carotene and xanthophyll. Carotene has only carbon and hydrogen atoms in its molecular structure, whereas xanthophyll has at least one oxygen atom (Fig. 3) ("Chemistry & Antioxidant Activity of Plants Containing Some Phenolic Compounds.", 2015).

Carotenoids are powerful antioxidants that efficiently scavenge ROS. Carotenoids, in particular, scavenge peroxyl radicals and protect lipids from peroxidation and damage (Oyenihi et al., 2014). Carotenoids, when combined with tocopherols, increase antioxidant activity in the lipid phase of the biological membrane more than tocopherols alone. Carotenoids have also been shown to scavenge oxygen, sulphur, and nitric radicals, as well as protect lipids from hydroxyl and superoxide radical attacks (Rahman, 2007). Carotenoids reduce peroxyl radicals to form a carbon-centered radical product that is resonance-stabilised. Lycopene, for example, reduces peroxyl radicals via electron transfer, resulting in an unreactive resonance-stabilised carbon-centered radical (Mortensen et al., 2001). It was also observed that a decrease in one of the synaptic vesicle proteins, synaptophysin, and brain-derived neurotrophic factor (BDNF), both of which are important in neuronal transmission activity and neuronal survival, was suppressed by lutein (carotenoids) treatment (M. Sasaki et al., 2010).

A number of studies have shown a strong correlation between carotenoids and DM (Akbaraly et al., 2008; Hozawa et al., 2006; Roohbakhsh et al., 2017; Sluijs et al., 2015). Carotenoids were found to have an inverse association with fasting plasma glucose concentrations, insulin resistance (Ylönen et al., 2003), serum insulin concentrations (Coyne et al., 2009), and HbA1c levels (Suzuki et al., 2002). A study conducted by Sasaki et al. (2010) showed that accumulated ROS in the STZ-induced diabetes model showed a significant reduction of ROS upon constant consumption of carotenoids in the diet. Furthermore, carotenoids supplementation in DM-induced animal models improved diabetic retinopathy (Kapucu, 2020; Yaribeygi et al., 2018) and basic haematological and immunological parameters (Eze et al., 2019). Carotenoids supplementation to diabetes patients reduced oxidative stress and improved immunity (Neyestani et al., 2007), improved visual function (Lem et al., 2021; Moschos et al., 2017), decreased inflammatory markers (Behrouz et al., 2021), and improved diabetic kidney disease (J. Zhang et al., 2023). Furthermore, a dose-response meta-analysis study concluded that higher dietary intakes and total carotenoids circulating concentrations were associated with a lower risk of T2DM (Jiang et al., 2021b). Carotenoids clearly have beneficial effects in DM not only by neutralising oxidative stress, but also through other mechanisms. Carotenoids have also been shown to reduce pancreatic inflammation and increase insulin resistance by modulating the immune system (Roohbakhsh et al., 2017).

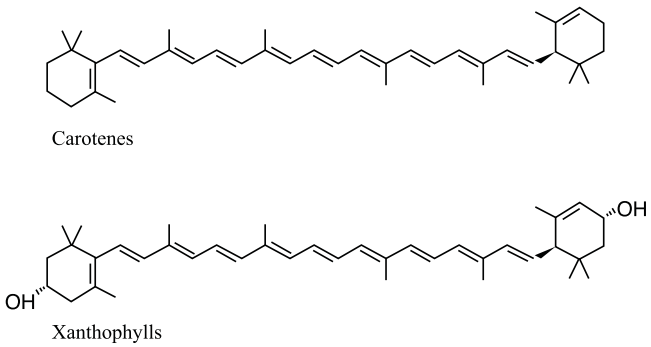


Fig. 3. Carotenoids.

Flavonoid

Flavonoids are low-molecular-weight secondary metabolites found in fruits and vegetables. It is a polyphenolic compound that, along with carotenoids, is responsible for the various colours of fruits and vegetables. Flavonoids have a 15-carbon skeleton that consists of two phenyl aromatic rings connected by a five-membered heterocyclic ring pyran in between two aromatic phenol rings. Flavonoids are classified into different classes based on the carbon of the C ring to which the B ring is attached, as well as the degree of unsaturation and oxidation of the C ring (Fig. 4). Flavonoids are well known for their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties, and have thus become an important component in pharmaceutical, nutraceutical, and cosmetic applications (Panche et al., 2016).

They act as hydrogen donors, reducing agents, metal chelating agents, and free radical scavengers due to their high redox potential (Walter & Marchesan, 2011). Polyphenolic flavonoids have been shown to protect DNA oligonucleotides from oxidative damage caused by H_2O_2, HO, and O_2, and to act as a cardioprotective substance by inhibiting lipid oxidation (Ratty & Das, 1988). Further, flavonoids such as rutin have been shown to reduce ROS formation and the precursors of advanced glycation end products (Ghorbani, 2017).

A study conducted by Jayasree et al. (2011) showed that epicatechin flavonoids act as insulin receptor activators and thus reduce the harmful effects of DM. Several studies have reported that flavonoid intake is inversely related to incidents of DM (Bondonno et al., 2021; Dinda et al., 2020; Guo et al., 2019; Yeon et al., 2015) and ameliorates its complications (Ghorbani, 2017). In a study treating diabetic mice for 45 days with flavonoid, naringenin showed improved glycaemic status, where hyperinsulinemia and hyperglycemia were significantly reduced (Annadurai et al., 2012). This is concomitant with the reports that showed flavonoids improve glucose homeostasis (Choi et al., 2007; Varshney et al., 2019). In various research conducted on an animal model of T2D using Ginkgo biloba L. (Ginkgoaceae) extract that is abundant with flavonoids as a treatment agent, it was shown that it induced insulin secretion (Choi et al., 2007), increased plasma insulin levels (Kudolo, 2001), and reduced glucose excursion after significant loading of glucose (Lim et al., 2011). Apart from the diabetic protective effect, Ginkgo biloba L. extract also showed effects on cardiovascular health, provision of mitochondrial protection, anti-platelet activity, anti-inflammatory effects, and anti-apoptotic properties (Haines et al., 2011; Smith et al., 2002). Further, flavonoids supplementation in diabetic rats showed restored insulin secretion and protection of pancreatic β-cells (Zhang et al., 2021b), improved insulin resistance (Tan et al., 2021), inhibited oxidative stress and inflammation, enhanced neurotrophic support in the brain (Ola et al., 2014), and impaired wound healing (Chen et al., 2021). In a systematic review and meta-analysis, studies showed that citrus bioflavonoid supplementation in T2DM patients had a positive impact on oxidative stress reduction and improvement in diabetes biomarkers (Gupta et al., 2023; Liu et al., 2021). A dose-response meta-analysis of flavonoids subclasses supplementation in the T2DM study showed that the risk of type 2 diabetes decreased by 2 % for every 100 mg/d increment in total flavonoids intake, decreased by 3 % for every 100 mg/d increment in flavonols intake, a 2 mg/day increment in intake of anthocyanins was associated with a risk ratio of 0.99, and decreased by 1 % for every 0.1 mg/d increment in isoflavones intake (Zhou et al., 2018).

Glutathione

GSH is a water-soluble tri-peptic antioxidant made up of the amino acids cysteine, glycine, and glutamic acid. GSH is produced in all plants and animals and synthesised in the liver. It is present largely in reduced form rather than oxidised form in the cell (Pócsi et al., 2004). Oxidised to reduced ratio increase in oxidative stress condition and decrease at a healthy state. GSH protects normal cells from oxidative injury by acting on free radical chain reactions and by serving as a cofactor in glutathione transferase, GPX, and glutathione reductase enzymes (Skowyra, 2014). GSH protects the biomolecules from superoxide anion, hydroxyl radical, nitric oxide, and carbon radicals, and thus it is vital in protecting from various clinical conditions like DM, neurodegenerative disorders, pulmonary diseases, immune diseases, cardiovascular diseases, chronic age-related diseases, liver disease, etc. GSH also takes part in vitamin C and E regeneration by donating hydrogen atoms (Rahman, 2007).

A study conducted by Kalkan and Suher (2013) showed that there is a significant reduction in GSH levels in diabetic patients compared to normal subjects. The study further showed that GSH levels are lower in patients with diabetic retinopathy than in patients not diagnosed with diabetic retinopathy. A decrease in the level of GSH occurs both due to the competition between aldose reductase and glutathione reductase for NADPH, cofactors during the polyol pathway, and increased oxidative stress by increasing the ratio of NADH/nicotinamide adenine dinucleotide (Pastore et al., 2003). GSH can also prevent increased levels of plasma cytokines induced by acute hyperglycemia and the PKC pathway (Esposito et al., 2002). Supplementation of GSH to animal models with DM resulted in reduced oxidative stress (Hermes-Uliana et al., 2018; Ueno et al., 2002) and preservation of in vivo renal and neural function (Hermes-Uliana et al., 2013; Ueno et al., 2002). T2DM patients supplemented with GSH showed reduced levels of oxidative stress in all blood components (To et al., 2021), reduced oxidative DNA damage (Kalamkar et al., 2022), decreased glycated haemoglobin (HbA1c) (Ghaskadbi et al., 2023; Kalamkar et al., 2022), improved insulin sensitivity (Søndergård et al., 2021), increased insulin secretion (Kalamkar et al., 2022), enhancements in immune function markers (Sinha et al., 2017), and replenished the body's stores of GSH (Kalamkar et al., 2022).

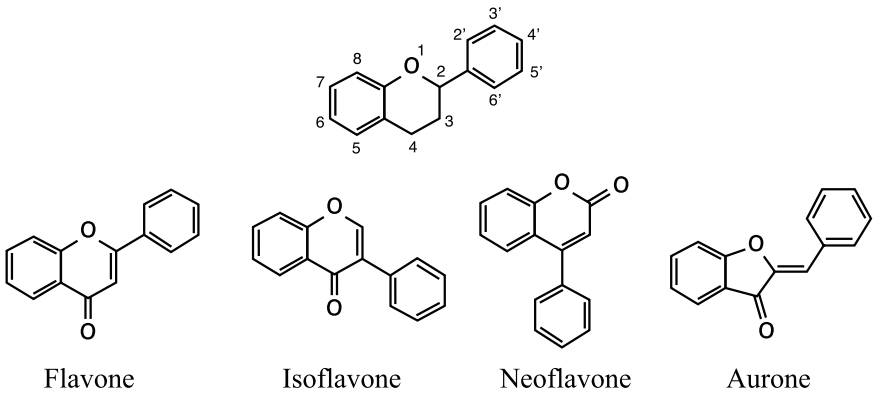


Fig. 4. Flavonoids.

Polyamines

PAs are aliphatic organic compounds that are present in all types of living cells and have more than two amino groups. They are naturally occurring polycations that interact with negatively charged DNA, ribonucleic acid, and proteins. PAs are vital for mammalian cell growth and development as they take part in multiple functions, including ion channel regulation, chromatin structure maintenance, DNA replication, transcription, translation, and radical scavenging. (Igarashi & Kashiwagi, 2010). Polyamines such as putrescine, spermidine, and spermine are biogenic unbranched PAs and exhibit antioxidant activity against hydrogen peroxide in red blood cells (Fujisawa & Kadoma, 2005). In physiological pH, PAs closely associate with DNA and proteins and protect them from oxidative damage (Rider et al., 2007). Due to the structure of PAs, they are also capable of preventing glycation by acting as antiglycan agents (Bjelakovic et al., 2010), and thus they are capable of preventing DM complications. PAs are present in the secretory granules of the islet β cells and responsible for proinsulin biosynthesis and insulin secretion (Kulkarni et al., 2022). Further, it has also been shown that the level of PAs in the islets decreases with age and obesity (Sjöholm et al., 2001), highlighting the importance of a PA-rich diet in patients with DM and old age.

Increased PA concentrations have been shown in numerous studies to have positive benefits in addressing the metabolic issues associated with obesity and T2DM (Castoldi et al., 2020; Ma et al., 2021; Monelli et al., 2022; Nakatani et al., 2022; Wang et al., 2021), and daily administration of PAs in obese mouse models resulted in weight loss and improvement of glycaemic levels (Fernández et al., 2017). In another study, administration of PAs to diabetic-induced rats showed improvement in glycaemia and a reduction in HbA1c (Méndez & Balderas, 2006). However, few studies have shown that PA depletion has a protective effect on T1DM in mouse models (Sims et al., 2023; Tersey et al., 2013).

In conclusion, PAs are important molecules that are necessary for β cells to operate normally. But it's important to maintain a balance because low and high PA levels have been linked to the development of diabetes and harmful effects on β cells (Kulkarni et al., 2022). Thus, more studies are warranted on the supplementation of PAs in DM to ultimately develop effective targeted therapeutics.

Conclusion

The prevalence and complications of DM are increasing day by day with today's lifestyles all over the world. At the cellular level, oxidative stress contributes significantly to pathogenesis of DM and the exacerbation of its complications. As a result, antioxidant supplementation in DM is becoming an important strategy in treating and reducing its complications. Further, antioxidant supplementation will also compensate for oxidative stress and protect against other complications such as cancer, Alzheimer's disease, cardiovascular disease and so on. In-vitro, pre-clinical, and human trials of antioxidants as a treatment for DM provided promising results in terms of DM progression and complications. Because of the safety concerns and other limitations associated with synthetic antioxidants, the use of antioxidant-rich vegetables and fruits is preferable to synthetic antioxidants. However, there are challenges in using antioxidant nutrients since they have limited absorption, can undergo auto-oxidation, and can be metabolised by gut microorganisms. Thus, more research is required to determine effective antioxidant treatment methods, effective doses of each dietary antioxidant, and the efficacy of antioxidant and drug combination therapy. Furthermore, the research reviewed in this paper indicates that the majority of these natural antioxidants are derived from plant sources, emphasising the novel research directions towards plant-based diets.

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CRediT authorship contribution statement

Mohamed Shafras: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rasangi Sabaragamuwa:** Conceptualization, Data curation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Mohamed Suwair:** Data curation, Resources, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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