Antioxidants in herbs and spices: role in diabetes mellitus

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Introduction:

Diabetes is a serious metabolic illness that is spreading around the globe. There are several elements contributing to the disease's etiology. Medical dietary therapy and medication are the mainstays of diabetic management. Using anti-inflammatory and antioxidant-rich spices has become commonplace since the field of medical nutrition treatment was established. As a result, their application in the management of diabetes has gained attention recently. The dried portions of plants are called spices. What distinguishes a spice from an herb is that an origin spice might originate from any part of the plant, although herbs always originate from the leaves (Zeb & Zeb 2021).

Spices are generally derived from dried plant parts, such as seeds (cumin), berries (cloves, chili, and black pepper), bark (cinnamon), buds and roots (ginger, turmeric) that have strong aromas or tastes and volatile oils. One of the most utilized plant spices, spices are used for both culinary and medicinal purposes. In terms of nutrition, spices are nutritional supplements mostly employed as food flavorings to enhance food flavor. In addition to preventing acute and chronic ailments spices can also improve the food's and beverages' flavor, fragrance and color (Sanlier& Gencer 2020).

One of the main factors lead to the development of diabetes is oxidative stress. The pathophysiology of diabetes is facilitated by oxidants overwhelming the antioxidant system, which is why diabetic people have a higher degree of ROS generation (more oxidative cells)

than do healthy subjects. Additionally, numerous investigations have shown a strong correlation among oxidative stress and diabetes mellitus (DM) because of elevated oxidative damage to essential macromolecules. According to studies, the type 2 diabetes mellitus (T2DM) condition and insulin-sensitive tissues have higher levels of protein carbonylation and nitrosylation.Furthermore, a few animal models have demonstrated a close correlation between increasing oxidative stress and protein unfolding, which results in the loss of protein function. Because of the oxidative stress, insulin resistance and insulin secretion are the two main processes that are altered in diabetic individuals. Oxidative stress is the cause of insulin resistance, which also inhibits insulin signaling and dysregulates adipocytokines (Unuofin& Lebelo 2020)

Antioxidants are molecules that stop, slow down or counteract oxidative damage to target molecules. Even in very small amounts, they hinder the oxidative process. Antioxidants are therefore the body's primary defense mechanism against damage from free radicals because the body produces free radicals as a result of several metabolic activities, and the body's homeostasis may be harmed by an unbalanced production and elimination of these free radicals. Numerous clinical ailments, including cancer, cardiovascular disorders, neurological diseases and diabetes have been linked to this imbalance (Poljsak et al., 2021)

Certain antioxidants, like superoxide dismutase (SOD), Catalase (CAT) and glutathione peroxidase (GPx) are produced by the body naturally. However a number of significant antioxidants are acquired by diet including fruits, vegetables and tea. Although these natural antioxidant systems aid in maintaining homeostasis by balancing the generation and removal of reactive oxygen species (ROS), free radicals and reactive nitrogen species (RNS), antioxidants found in food have also been linked to enhancing free radical/antioxidant homeostasis, which may decrease the risk of cancer, cardiovascular complications, aging and diabetes (Oluwole &Ademuyiwa 2021).

Herbs and spices continue to behelpful in the treatment and prevention of a variety of diseases. They offer a wealth of resources for the identification of novel compounds with particular structural arrangements that exhibit promising therapeutic properties for the management of various diseases. Generally speaking, pharmaceuticals derived from these sources are believed to be more affordable, accessible, secure, and occasionally even more effective than those made completely of synthetic materials (Patel et al., 2022).

Researchers have been looking for the safest and most effective natural medications in recent years, particularly through herbs and spices from medicinal plants.Type 2 diabetes mellitus, in particular, is spreading over the world at an alarming rate and in an increasing order. Improvements in glycemic control reduce the risk of developing diabetes mellitus. It is important to discover new and efficient prospective agents with enhanced potency and fewer side effects because the anti-diabetic medications now in use are associated with a few serious adverse effects (Patle et al.,2021).

Symptoms and types of diabetes

The main symptoms of diabetes mellitus are primarily elevated blood sugar level, excessive thirst (polydipsia) and extreme hunger (hyperphagia). Diabetes mellitus is one of the most prevalent metabolic disorders and it is increasing terribly around the world. The number of DM patients has increased fourfold in just 34 years (from 108 million in 1980 to 422 million in 2014), while the global incidence of diabetes among persons over 18 has increased from 4.7% in 1980 to 8.5% in 2014. World health organization (WHO) estimated that by 2030, diabetes would rank as the seventh most common cause of mortality (Kumar et al., 2020).

Four primary types of DM are commonly observed. Type 1 diabetes (T1DM) is caused by the autoimmune destruction of pancreatic β- cells, which leads to inadequate generation of insulin. This type is also called insulin dependent diabetes mellitus (IDDM). Five to ten percent of all diabetic patients have this kind of diabetes, which is prevalent in children. The most common kind of diabetes is type 2 diabetes (T2DM) it occurs due to desensitization of insulin receptors and inadequate production of insulin, which blocks the cells ability to absorb glucose. This type is most commonly observed in 90-95% of cases (Eizirik et al., 2020)

Gestational diabetes mellitus (GDM) is another form of diabetes that only appears during pregnancy. Pregnant women with GDM account for 5-15% of cases, with regional and ethnic variations. This form of diabetes is caused by a variety of conditions, such as genetic flaws, pancreatic destruction, and surgery and organ transplantation. In this case, 5-10 years after giving birth, 40-60% of women with GDM can develop DM. Uncontrolled diabetes may lead to the development of numerous other diseases including peripheral neuropathy, hypertension, myocardial infarction, visual impairment, kidney failure and encephalopathy. Another form of DM is Neonatal diabetes mellitus or familial diabetes mellitus. Neonatal diabetes mellitus, which typically appears before the age of 6 months, can be temporary or

chronic. DM can be treated and its problems can be reduced by adhering to a healthy diet, engaging in physical exercise, taking the prescribed medicine and routinely checking the condition (Alam et al., 2021).

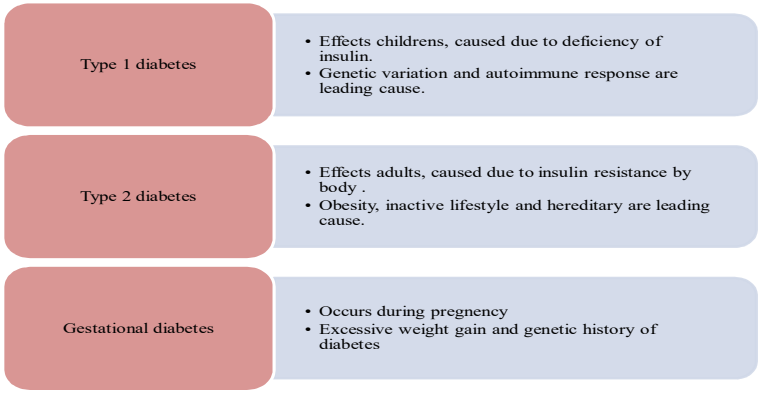

Figure 1: Different types of Diabetes.

How oxidative stress leads to diabetes mellitus

Beta cell activity is compromised by oxidative stress through a number of molecular pathways. Proinsulin vesicles are not incorporated into the plasma membrane, significantly less insulin is generated, and their exocytosis in response to glucose entering the bloodstream is reduced. Moreover, it can cause apoptotic processes in pancreatic cells, which can result in beta cell loss and death. A number of proapoptotic substances can induce apoptosis in pancreatic cells and are extremely sensitive to oxidative stress. Furthermore, an excess of free radical species disrupts KATP channels and negatively impacts beta cell metabolic pathways, which lowers insulin output (Charlton et al., 2020) By adhering to their SH residues, free radicals cause damage to KATP channels, as evidenced by research showing that beta cell KATP channel deletion models protected the cells from oxidative stress. Increased free radical concentrations reduce insulin production at the DNA level by inhibiting nuclear

transcription factors such as MafA, a transcription factor, and Pdx-1 and insulin promoter factor 1 that are involved in insulin gene expression. In 2017, Wang and his coworkers showed that oxidative stress triggered molecular pathways including hexosamine pathways, JNK\SAPK, p38 MAPK and Nf-κb. In beta cell failure, these stress-activated signaling pathways play a critical role. Additionally, free radicals have the ability to activate tall like receptors (TLRs), which subsequently impair beta-cell function (Yaribeygi et al 2020).

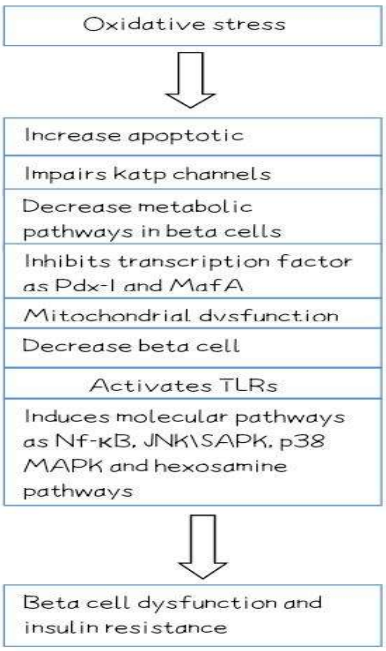

Figure 2: Potential biological pathways that connect beta cell dysfunction and oxidative stress to cause diabetes mellitus.

The link between antioxidant and diabetes mellitus:

As an effective treatment has not yet been found, diabetes management remains a global issue. Diabetes mellitus treatment has completely changed with the advent of insulin and thereafter oral hypoglycemic medications. Despite progress in managing diabetes with medications, complications and severe drug reactions persist. Clearly, none of them were able to keep their blood glucose levels within normal range and prevent any consequences. While several synthetic medications have been produced for patients, no one has ever been reported to have fully recovered from diabetes.Approximately 200 pure substances originating from plants have been shown to have a reducing effect on blood glucose levels. These substances could include lipids, phenolics, glycopeptides, iridoids, alkaloids, flavonoids, steroids, terpenoids, and amino acids and peptides (Black, 2022).

According to the American Diabetes Association (ADA, 2002), people with diabetes should be informed about the significance of obtaining sufficient levels of vitamins and minerals from natural food sources, such as herbs and spices, and are advised against taking routine doses of synthetic antioxidants. Additionally, antioxidants are frequently included as components of dietary supplements with the aim of preserving health and averting illnesses. For thousands of years, traditional remedies have utilized dietary agents derived from herbs and spices, which are composed of a diverse range of physiologically active chemicals found in plants (Moosavi-Movahedi et al., 2021).

Several research have been conducted on the effects of various substances as antioxidants, including natural antioxidants derived from plants because; oxidative stress is significant for many DM problems. Consequently, information was gathered about the function of several antioxidants, including glutathione, coenzyme Q10 and α-lipoic acid in regaining insulin sensitivity. Studies have demonstrated the significant reduction of diabetes complications by α and γ-tocopherol, retinol, β-cryptoxanthin, ascorbic acid, α and β- carotene and lutein. More

than 10,000 phytochemical components of food and medicinal plants have been identified. It has been demonstrated that these compounds have strong anti-inflammatory and antioxidant properties, control the actions of lipase and α-glucosidase, lower blood sugar enhance pancreatic function, work in combinations with hypoglycemic medications, and are therefore very effective in treating diabetes mellitus (Deng et al., 2021).

Role of herbs and spices in managing diabetes mellitus:

The past few decades, research on health benefits of herbs and spice has increased significantly because many of them are recognized to have qualities that lower the chance of developing chronic diseases. Furthermore, a number of possible health advantages of herbs and spices include defense against cancer, obesity, arthritis, neurological disease, heart disease and type 2 DM. It has also been noted that a variety of herbs and spices possess potent anti-inflammatory, anti-microbial and anti-oxidant qualities. A survey conducted by the WHO revealed that 70-80% of people worldwide mostly receive their primary medical care from herbal sources rather than modern medication. In addition, 80% of people in underdeveloped nations and as much as 60% of people worldwide rely only on plants and herbs for medical purposes (Chaudhari et al., 2021).

Given with the complexity of DM, agents with many targets are needed rather than a single target approach by a single drug. Given that several agents can be used to modulate different protein targets, plants like herbs and spices offer a very profitable treatment option for diabetes mellitus. Study revealed that nearly 50% of the herbs and spices had a substantial percentage of multiple targets, including liquorice, cinnamon, cumin, fennel, fenugreek, oregano, lemon grass, saffron and thyme (Shenoy et al., 2022).

The primary anti-diabetic action observed in previous studies included reductions in hyperglycemia and hyperlipidemia as well as regulation of insulin secretion. Therefore, extracts derived from these herbs and spices have the potential to completely restore the impaired functions associated with diabetes. For example, research conducted in vivo has shown that rosemary therapy modifies the function of glucokinase (GCK) and Fructose 1, 6 bisphosphate (FBP1). Many flavonoid glucosides, including 6-hydroxyluteolin-7-o-glucoside, Apigenin-7-o-glucoside, hispidulin-rutinoside, hesperidin and luteolin-7-o-glucoside and luteolin-7-o-rutinoside, were discovered to be functioning as possible inhibitors of FBP1 in relation to rosemary's inhibition to this enzyme. Alpha- glucosidase

inhibitory activity has also been linked to rosemary treatment in in-vivo and in-vitro experiments (Kaur et al.,2020).

Table: Bioactive compounds of herbs and spices with anti-diabetic effects (Chandra et al., 2020)

Herbs and spices	Bioactive compounds
Cinnamon (*Cinnamomum*)	Cinnamaldehyde, Procyanidin
Indian berberry(*Berberis aristata*)	Berberine, berbamine, aromoline andpalmatine
Turmeric (*Curcuma longa*)	Curcumin, caffeic acid and coumaric acid
Cumin (*Cuminum cyminum*)	Cuminaldehyde, cuminol, apigenin and luteolin
Castor oil plant (*Ricinuscommunis*)	Ricinine, kaemferol, quercetin andrutinoside
Clove (*Syzygium aromaticum*)	Eugenyl acetate, eugenol and β-caryophyllene
Garlic (*Allium sativum*)	Allicin, caffeic acid, vanillic acid, hydroxybenzoic acid
Fenugreek (*Trigonella foenum graecum*)	Saponin
Zinger (*Zingiber officinale*)	curcumen, zingiberene and gingerols
Neem (*Azadirachta indica*)	Azadirachtin, Nimbin

Antioxidant rich herbs and spices:

Many varieties of herbs and spices contain components that are typically safe for human health, and their advantages have long been recognized. These advantages include aid in digestion, anti-inflammatory, antirheumatic, antisclerotic, antiallergic and antidiabetic properties. Owing to their advantages, they find application in numerous acute and chronic illnesses, including cancer, diabetes mellitus, hypertension, liver cirrhosis and arthritis.Spices and herbs are also utilized to enhance the taste, aroma and nutritional content of food, provide protective properties during storage and prolong its shelf life (karakul & Kapi 2021).

(1) Cumin (*Cuminumcyminum*):

It is typically used to add flavor to a variety of food items, such as cheese, soup, dishes pickles and liquors. This spice contains the highest concentration of minerals including copper, potassium, iron, manganese, calcium and selenium. It also has high amounts of B-6, niacin, thiamin and riboflavin among other vitamins. It also contains a few other essential antioxidant vitamins, such as vitamin C, E and A. In Hindi, *C. cyminum* is referred to as

Jeera, and in Sanskrit as Jeeraka. This plant has several names in several languages, such as Zeera in Punjabi, Cumin in English, Jire in Marathi, Jira or Zeera in Hindi, Jeera in Gujrati and Zirgaum in Tamil (Allaq et al., 2020).

The oil of *C. cyminum* demonstrates notable levels of antioxidant components with strong antioxidant activity, and its nonvolatile extracts demonstrate good inhibitory activities against free radicals. Comparing methanol extracts to n-hexane extracts, it is discovered that the former exhibits stronger antioxidant activity. Flavoring agents and new natural antioxidants that can be employed in a variety of culinary products can be produced from this spice. The primary component of essential oil, cuminol, is found in *C.cyminum* fruits, which have an oil yield of 2.5 to 4% of their weight. *C.cyminum* exhibits a higher antioxidant potential, which makes it a beneficial source of natural antioxidants. So it is concluded that *C.cyminum* has good antioxidant potential. Methanolic extract from *C.cyminum* seeds preserves glycosylated hemoglobin, lowers blood glucose, creatinine, blood urea nitrogen and increase serum insulin and glycogen (Mughal, 2022).

(2) Cinnamon (*Cinnamomum verum*):

The United States food and Drug Administration (FDA) has classified cinnamon as GRAS (generally recognized as safe), making it one of the world's most used spices. As shown by numerous research, Cinnamaldehyde, A-type procyanidin, and B-type procyanidin are in abundant in cinnamon. Several health benefits of cinnamon include its anti-inflammatory, antibacterial and antioxidant, anti-pyretic and anti-ulcer properties. 1n 1990, it was reported that cinnamon can also be used for managing diabetes (Banaszak et al., 2024).

This demonstrates that cinnamon contained insulin potentiating factor (IPF)and also suggested that IPF might be helpful in reducing the symptoms of diabetes and other conditions linked to insulin resistance. *Cinnamomum burmanii, Cinnamomum zeylanicum, cinnamomum cassia and cinnamomum verum* are the cinnamomum species that have been found to be improving in glycemic response. Out of these, *cinnamomum cassia*, sometimes known as Chinese cinnamon, has the best profile for managing elevated blood sugar in individuals with type 2 diabetes (Shang et al., 2021).

Cinnamon is said to lower blood sugar and cholesterol level via a number of different pathways. These strategies include regulating glucagon-like peptide 1 (GLP-1), decreasing glucosidase activity, delaying stomach emptying and inducing insulin secretion or insulin

mimetic. Research conducted in-vitro revealed the polyphenol chemicals (A-type procyanidin) isolated from cinnamon possessed characteristics like those of insulin, which could hinder the action of PTP-1 (Protein tyrosine phosphatase) or the serine phosphorylation of IRS-1 (insulin receptor substrate-1) . Therefore, it was proposed that cinnamon could be helpful in the management of conditions linked to insulin resistance and metabolic syndrome (Bi et al., 2017).

(3)Clove (*Syzygium aromaticum*):

Syzygium aromaticum, also referred to as clove belongs to Mirtaceae family is thought to have originated in the Eastern Indonesian Maluku islands. It is the dried flower bud of medium sized tree. The West Indies, Madagascar, Tanzania, India and Sri Lanka are the main producers of this spice. Humans have utilized cloves for their therapeutic benefits for at least 2,000 years. Historically, the oil has been utilized as an antibacterial, antiallergic, antidiabetic and for dental issues particularly toothaches. The leaves and the buds of *S.aromaticum*can yield essential oils, and the essential oils derived from each source have different compositions.Nevertheless, it has been discovered that the primary constituents are β-caryophyllene, eugenol and eugenol acetate. Because of their wide range of phytoconstituents, cloves are employed as a spice in culinary applications as well as in nutraceuticals (Ruyati&Ruyati 2024).

> Due to its high content of phenolics, such as eugenol and eugenol acetate, clove has been shown to be a powerful antioxidant. In in-vitro study Clove and butylated hydroxytoluene (BHT), a synthetic food preservative, were compared for their antioxidant properties. The 1, 1-diphenyl2-picryl hydroxyl (DPPH) radical, ferric thiocyanate, hydroxyl radical and reducing power model systems were used to measure the antioxidant activity (Radunz et al., 2021).

Clove's ability to scavenge free radicals and other spices in both aqueous and alcohol extracts revealed that flavonoids and phenolic components were responsible for their antioxidant potential. Many spices inhibit lipid peroxidation in dose dependent manner, but the clove has highest level of action. Clove oil inhibits the formation of triggered reactive oxygen species (ROS) and nitric oxide in human neutrophils, whereas it exhibits a high level of myeloperoxidase (MPO) inhibition in human leukocytes (Mehrotra, 2021).

(4) Fenugreek (*Trigonella foenum graecum*):

Within the Fabaceae family, *Trigonella Foenum graecum* is considered one of the most effective plants in traditional medicine for treating diabetes. It has been demonstrated that *Trigonella*reduces blood glucose in healthy and diabetic animal models in a dose dependent maner. Furthermore, in vitro studies revealed that the compound 4-hydroxyl lysine isolated from *Trigonella* provokes the pancreatic island cells to release more insulin in response to glucose both in mice and humans. This result in an increase in receptors accompanied by an inhibition of the activities of intestinal enzymes involved in the metabolism of carbohydrates, alpha amylase and sucrase. Amongst the substances found in the plant seeds of fenugreek are mucilages, flavonoids, saponins and volatile alkaloids. One of the major therapeutic effects on diabetes by fenugreek seed is due to its direct stimulatory effect on the release of insulin from beta cells by an amino acid, 4-hydroxyisoleucine (Sarwar et al., 2020).

Changes in some of the bioactive chemical components of fenugreek seeds, which serves as building blocks, are principally responsible for their pharmacological and biological properties for various hormone-based and therapeutic medicines. Fenugreek seeds are used in traditional medicine for the cure of hypercholesterolemia and diabetes because of the main content of lysine and L-tryptophan in their proteins and other biochemical constituents like saponins, coumarins, and sapogenins. Fenugreek seed is a potential nutraceutical that has been the focus of several recent laboratory and clinical studies (Alsieni et al., 2021).

It contains several bioactive components, and others have antiperoxidative with polyphenolic flavonoids and hypoglycemic characteristics. In addition to this, fenugreek seeds contain polysaccharides like galactomannan, having anti-diabetic properties, and the amino acid 4-hydroxyisoleucine with insulin-mimetic properties. Besides, it has antioxidants, gastro, and hepatoprotective and immunomodulatory effects. Moreover, it restitutes the normal blood flow that sustains the system in function. Fenugreek seeds' activities at a pharmacological level are thought to be involved in maintaining cardiovascular health and managing diabetes, an indication that there might be some bioactive compounds responsible (Srinivasa & Naidu 2021).

(5) Garlic(*Allium sativum*) :

Garlic, or *Allium sativum Linn.,* is a very common herb that belongs to the *Allium* family. It can be found throughout Europe, Africa, and Asia. Originally native to Asia, it has only recently gained appeal as a condiment, particularly for Asian cooking. Their uses demonstrate

garlic's potent therapeutic properties which have been in use for more than a thousand years to cure a wide range of illnesses. It has been shown in many scientific studies that garlic contains many biological properties, such as anti-tumor and antibiotic activity with anti-microbial activity having anti-hyperglycemic activity (Tran et al., 2020).

Raw garlic is rich in potent phytochemicals, primarily alkaloids, flavonoids, cardiac glycosides, terpenes, steroids, and resin. Some sulfur-containing compounds are also present in it, such as minerals, enzymes, B-vitamins, proteins, saponins, flavonoids, ajoene, and alliin. Different scientific studies have proved garlic's biological activity against diabetes prevention, where its mechanism of action has been described to involve improvement in glucose tolerance, modulation of insulin secretion from β-cells, and glycogenesis. For instance, certain bioactive compounds isolated from garlic, specifically allyl propyldisulfide and S-methylcysteine sulfoxide, decreased blood sugar levels. Moreover, ethanol extract from garlic exhibited anti-diabetic activity through the reversal of the delayed response of insulin (EI-Saber et al., 2020).

(6) Turmeric (*Curcuma longa*) :

Turmeric, or *Curcuma longa*, is a perennial herb that is widely grown throughout Asia, primarily in China and India. Botanically, it belongs to the ginger family of Zingiberaceae. Its rhizome gives out a bright yellow powder and it is used as the medicinal part of the plant. It goes by many names: Indian saffron, Haridra in Sanskrit and Ayurvedic, Jianghuang in Chinese—yellow ginger, Curcum for the Arabs, and Kyoo, otherwise known as "Ukon" in Japanese. Turmeric is used for its flavor and color in Asian cuisines and, more recently, as an anti-diabetic and anti-inflammatory and in the treatment of jaundice, hematuria, bleeding, constipation, and diarrhea by Chinese and Ayurvedic medicine. The active ingredients in turmeric are flavonoid curcuminoids: a mixture of curcumin, monodexmethoxycurcumin, and bisdemethoxycurcumin, the latter constituting about 90% of this curcuminoid fraction. Some of the added constituents include resins, proteins, and carbohydrates (Iweala et al., 2023).

For treatment of diabetes mellitus a mixture of honey, amla juice and powdered turmeric rhizome is particularly beneficial. 6grams of *curcuma longa* increased postprandial serum insulin levels in healthy adults, but it does not seem to affect GI or plasma glucose levels. The findings suggest that *curcuma longa* may have an impact on insulin secretion. The active ingredients in the rhizome of the turmeric plant are called curcuminoids and they prevent lipid per-oxidation by maintaining higher levels of antioxidant enzyme activity. These

include glutathione peroxidase, catalase, and superoxide dismutase. According to Karigidi et al. (2022), curcumin and three of its derivatives, including demethoxy curcumin, bisdemethoxy curcumin, and diacetyl curcumin, comprise the antioxidant activities of *C. longa* (Karigidi et al., 2022).

The freeze-dried rhizome powder of *curcuma longa* in milk demonstrated hepatoprotactive, hypolipidemic and anti-diabetic effects; therefore, it could turn out to be one of the most potent and safe dietary supplements against diabetes. Between known flavonoids, terpenoids, glycosides, and curcuminoids of*C. longa*, isopropanol and acetone extracts exhibited a maximum degree of inhibition on the HPA enzyme. This HPA inhibitory activity results in reduced hydrolysis of starch, subsequently lowering the levels of glucose (Razzaq et al., 2020).

(7) Indian barberry (*Berberis aristata*):

The common names for *Berberis aristata* are Indian barberry, Tree turmeric, Daruharidra, Daru Haldi, and Chitra. It belongs to the Berberidaceae family. This is a hardy, spiny herb with a yellowish hue that is a member of the Berberidaceae family. The main growing areas of this plant are the Nilgiri hills in southern India, the sub-Himalayan region, and hilly regions of Nepal up to an altitude 2000–3500 meters. It is regarded as the most important herbal plant because of its therapeutic value in Siddha, Unani, and Ayurvedic systems of medicine. The roots of the plant are the authenticated source of medicine. This plant has been in use for quite a long as a tonic, demulcent, diaphoretic, diuretic, and alterative for treating several diseases, including rheumatism, diabetes, snakebite, wound healing, and skin diseases, along with jaundice and problems of the eyes (Choudhary et al., 2021).

One of the main anti-diabetic compounds from this plant is berberine. It has been suggested that berberine may function through insulin-mimetic pathways, increasing the action of insulin by activating 5’ adenosine monophosphate activated protein kinase and decreasing insulin resistance by upregulating the expression of insulin receptors in a protein kinase C-dependent way, inducing glycolysis, and increasing the secretion, controlling the release of GLP-1, and inhibiting DPP-IV. In a study, it was reported that 0.5 gm of berberine obtained from B. aristata taken three times a day by type 2 diabetes patients reduced HbA1c, postprandial blood glucose, postprandial insulin, basal insulin and fasting blood glucose to almost the same extent as metformin monotherapy (Belwal et al., 2020).

In another clinical research, berberine showed itself to be useful in patients with poorly controlled type 2 diabetes as adjuvant therapy. In other clinical trials, berberine demonstrated promising efficacy in reducing HbA1c, fasting blood glucose, and postprandial blood glucose compared to rosiglitazone and metformin, although it exerted some negative effects on the liver. In another randomized-controlled trial of six months on 85 patients with type 1 diabetes (39 males and 46 females), a twice-daily tablet containing a 588/105 mg combination of Berberis aristata and Silybum marianum was found to decrease the body's use of insulin in cases of insulin therapy (Roshanravan et al., 2023).

(8) Castor oil plant (*Ricinus communis*) :

Ricinus communis was a commonly used traditional herbal remedy in the management of type 2 diabetes. It isErandah in Sanskrit, Amudam in Telugu, Arandi in Hind, and more commonly known as castor oil. This had been cultivated all over India for its seed oil and belongs to the Euphorbaceae family. Various plant parts are used in Indian medicine for treating hepatic and inflammatory conditions. In the preliminary screening trials, 50% of ethanolic extract of this plant's root, stem and leaves showed hypoglycemic effects in normal mice and anti-hyperglycemic activities in diabetic rats. Blood glucose levels in diabetic rats were significantly lowered by ethanolic extract after long-term treatment, while the blood glucose of control animals remained the same (Kumar et al., 2023).

During this all, the 50 % ethanolic root extracts of *Ricinus communis* exhibited a dose-dependent response on blood glucose of diabetic rat up to a dosage of 500 mg/kg body weight It had been found to exert a potent lowering action on blood glucose levels of both alloxan-diabetic and normal rats. In *Ricinus communis*, the effective dosage was established to be 500 mg/kg body weight. When this ethanolic extract was given to diabetic rats for 20 days, the rat's blood glucose levels significantly decreased to near normal; their body weight and lipid profile improved significantly. Moreover, the insulin levels were found to be higher. It holds great promise for the development of a strong phytomedicine against diabetes (Abomughaid et al., 2024).

Another study demonstrated the anti-diabetic effects of ethanolic and aqueous-ethanolic extract of *Ricinus communis* leaves in streptozocin induced diabetic rats. When given to diabetic rats for 14 days at a dose of 300 and 600 mg/kg body weight, the ethanolic and aqueous-ethanolic extracts demonstrated positive outcomes. At dosages of 300mg/kg/BW, both extracts exhibited excellent reversal body weight loss properties. The ethanolic extract significantly decreases blood glucose levels at 600 mg/kg/BW. When this extract given

orally, the extract (600mg/kg/BW) prevented changes in albumin, urea, creatinine, total proteins and total bilirubin levels which makethis, extract a very promising candidate to be used for the regulation of diabetes mellitus (Chouhan et al., 2021).

(9) Neem (*Azadirachta indica*) :

Other names for Azadirachta indica include Indian neem and margosa tree. It is constantly used since ancient times in homoeopathic, unani, and ayurvedic treatment.The tree is also known as "Sarvaroganivarini," which in a direct translation means "cure all ailments." Neem in Ayurveda is termed as "Arishtha, which means "reliever of sickness." Because of the presence of its medicinal features, the tree is still called today in India a "Divine tree" or a "village pharmacy." Currently, more than 150 compounds have been identified from different parts of this plant. Based on this structure, the compounds typically synthesized by this plant can be grouped into the following: isoprenoids, to which diterpenoids and triterpenoids belong, and which specifically include C-secomeliacins such as nimbin, salanin and azadirachtin, as well as protomeliacins, limonoids, gedunin and derivatives, azadirone and vilasinin-derivatives; with proteins, carbohydrates (Islas et al., 2020).

Extracts from neem leaves have demonstrated efficacy in lowering plasma glucose levels and in preventing increases in blood glucose from glucose and adrenaline challenge. Leaf extract and seed oil recently were determined to have anti-hyperglycemic effect in rats with diabetes caused by alloxan. An earlier study showed that when given 250 mg/kg B.W of neem extract, diabetic rats exhibited noticeably reduced blood glucose levels compared with the control. Neem root bark extract decreased blood sugar at both 200 and 400 mg/kg/B.W dosages. The higher dosage of this extract significantly reduced blood sugar levels as compared to a control with it reducing 54% at the amount of 800 mg/kg B.W. Glibenclamide was also used together with neem kernel powder alone or combined as an antidiabetic treatment against lab animals. The results showed that these two materials caused a marked decrease in fasting serum glucose, lipids, and activity of serum enzymes (Reddy & Neelima 2020).

Neem root bark extract with 70% alcohol content has been screened for its actions on diabetes, and the outcomes demonstrated that the 800 mg/kg of extract dosage exhibited statistically significant action. Another study was carried out to investigate *Azadirachtaindica's* pharmacological hypoglycemic effects on rats with diabetes. The outcomes showed that, in a glucose tolerance test with 250mg/kg neem extract, the test group

had significantly lower blood glucose levels than the control group, and this is noticed that on the fifteenth day, *Azadirachta indica* significantly lowered the glucose levels in the diabetic rats. Investigation on the diabetic murine model was performed for evaluation of the in vivo A. indica and B. spectabilis chloroform, methanolic, and aqueous extracts. The findings revealed that both extracts considerably decreased intestinal glucosidase activity and showed good oral glucose tolerance. (Patil et al., 2022).

(10) Ginger (*Zingiber officinale*) :

Ginger is among the oldest spices and medicinal herbs. Common ginger— Gingiber officinale is an herbaceous plant of the Zingiberaceae family, having a strong rhizome divided into tuberous parts. Its leaves are lanceolate, with a length of 5-30 cm and width of 8-20 cm, with stems growing up to 1.5 meters. Numerous tropical nations, including Africa, China, India and Jamaica cultivate it, and it originally came from Southeast Asia. Ginger root is easily available throughout Europe, primarily used together with Asian cuisine. Ginger contains a lot of essential oils. One to three percent is present in the rhizome. Among more than fifty discovered essential oils, two should be noted in particular: sesquiterpenes (ar-curcumen and α-zingiberene 30–70%, β-sesquifelandrene 15–20%, β-bisabolene 10–15%, zingiberol) and monoterpenes. Fresh ginger gets its spicy flavor from gingerols, while the spicy flavor of dried ginger originates from shoagols, which are dehydrated forms of those mentioned earlier (Przeor, 2022).

The literature abounds with research using different models to demonstrate the antidiabetic effect of ginger. When ginger extract (4mL/kg body mass per day) was given to diabetic rats for six weeks, the animal's blood glucose levels were considerably reduced. Flattening of the blood glucose and insulinemia curves in the group of diabetic rats during the glucose tolerance test was observed after the consumption of 4 mL of ginger juice per kg per day for six weeks. After giving rats 100-500mg/kg of aqueous ginger extract for 30 days, the animals' glycolytic enzyme activity increased and the extract had ant-hyperglycemic effects. A nephroprotective effect resulted from 30-day administration of 200mg/kg of ethanolic ginger extract in the animal diet, which also increased the activities of extra and intra-mitochondrial enzymes and reversed hyprglycemia. In rodents ginger improves insulin sensitivity, maintains pancreatic β-cells and lowers oxidative stress(Otunola& Afolayan 2020).

Mechanism of action how antioxidants combat diabetes mellitus:

Antioxidant defense mechanisms are classified as either non-enzymatic or enzymatic. There are two types of antioxidant defense mechanisms: enzymatic and non-enzymatic. Vitamin A, C and E, glutathione, mixed carotenoids, Coenzyme Q10 (CoQ10), a number of bioflavonoids, antioxidant minerals (copper, zinc, manganese and selenium) and cofactors such as folic acid, albumin and vitamins B1, B2, B6 and B12 are examples of common non-enzymatic antioxidants. Enzymatic antioxidants include SOD, CAT and GPx.Antioxidants influence signal transduction, proliferation regulation and the immune response through regular physiological processes. Even though reactive oxygen species (ROS) have been connected to cardiovascular disease (CVD) diabetes and cancer,antioxidants have demonstrated a promising therapeutic approach for the prevention and management of these complications (Khutami et al., 2022).

In a clinical trial investigation, 36 T1DM patients were evaluated by Bursell. Participants in this crossover trial were split into two groups: the first received high dosage vitamin E supplementation (1800IU\day), while the second group received a placebo. This study's main goal was to ascertain whether vitamin E may help individuals with type 1 diabetes to restore normal retinal blood flow and kidney functions. Without significantly altering glycemic management, they discovered oral vitamin E therapy appeared to be beneficial in normalizing retinal hemodynamic abnormalities and restoring renal function in T1DM patients, particularly those with short disease duration. This shows that taking supplements of vitamin E may also help in lowering the chance of developing diabetic retinopathy or nephropathy. Vitamin C supplements are useful in lowering the accumulation of sorbitol in diabetic's red blood cells (Bhatti et al., 2022).

Conclusion:

Diabetes is a global metabolic illness with various factors as contributors. Medical dietary therapy and medication are the basics that lead to diabetic management. This chapter has focused on the role that oxidative stress plays in diabetes mellitus and the role antioxidants play in reducing the disruption that free radicals cause. It has been indicated that diabetes is correlated with oxidative stress, which is associated with decreased insulin action and an increase in the frequency of complications. Elevation of oxygen and nitrogen free radicals is directly associated with the oxidation of glucose, non-enzymatic glycation of proteins, and lipid peroxidation, which causes diabetes mellitus. Herbs and spices include many different compounds having antioxidant action. Plants and herbs have a lot of antioxidant parts which

may be pharmacologically useful in managing diabetes and its effects. Plants with anti-diabetic properties are well known, and only a few plants with such properties have been discussed herein. Anti-diabetic effects of those plants are mediated either by stimulating the pancreas to secrete insulin, interfering with the absorption of glucose, or due to an insulin-sparing bioactive ingredient.

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