Therapeutic Potential in Diabetes and Diabetes Associated Problems: A Comprehensive Review

Abstract-

Diabetes prevalence has increased dramatically in almost every part of the world in recent decades. The increased number of persons with diabetes or those who have had diabetes for a longer period is anticipated to change the disease profile in many communities throughout the world, owing to a higher frequency of diabetes-specific comorbidities such as kidney failure and peripheral artery disease. The epidemiology of other illnesses commonly linked with diabetes, such as infections and cardiovascular disease, may also shift, with significant consequences for the quality of life, healthcare needs, and economic expenditures. Diabetes (DM) is becoming more common at an alarming pace throughout the world. According to the International Diabetes Federation, an estimated 415 million individuals worldwide suffered from this illness in 2015. Diabetes complications include increased morbidity, disability, and death, posing a danger to the economies of all countries, particularly emerging ones. The current understanding of the global burden and variance in diabetes-related complications is inadequate. According to the available statistics, rates of myocardial infarction, stroke, and amputation are falling among diabetics, coinciding with lower mortality. However, the majority of these statistics originate from research conducted in only a few high-income nations. Other diabetic consequences, such as end-stage renal disease, retinopathy, and cancer, have received less attention. Obesity, insulin resistance, hyperglycemia, and hyperlipidemia are all variables that influence the development and progression of diabetes problems. In this review, we have included all the major complications and their pathophysiology along with their possible mechanism of action and the possible treatment with herbal or medicinal plants. This review will explore new ways of the diabetic complications around the globe.

Keywords- Diabetes, Diabetic complications, Herbal drugs, Mechanism of action.

Introduction-

Diabetes was expected to affect more than 20 million persons in the United States in 2005. Approximately 30% of these individuals were undiagnosed. Diabetes risk factors include age, ethnicity, a family history of diabetes, smoking, obesity, and physical inactivity. Diabetes-related consequences, such as cardiovascular disease, renal disease, neuropathy, blindness, and lower-extremity amputation, are a substantial cause of increased morbidity and death among diabetics and impose a significant financial burden on the US healthcare system. Diabetes patients are enjoying longer lives because of breakthroughs in therapy for the disease and its consequences. This increased life expectancy will lead to significant rises in diabetes morbidity, particularly among the elderly and minority racial or ethnic groups (Anjali D Deshpande, Marcie Harris-Hayes, 2008). Diabetes macrovascular complications, such as coronary heart disease, stroke, and peripheral vascular disease, and microvascular complications, such as end-stage renal disease (ESRD), retinopathy, and neuropathy, as well as lower-extremity amputations (LEA), account for the majority of the burden [38].

a) Epidemiology and Pathogenesis of Diabetic Complications-

There is mounting evidence that specific genetic and epigenetic changes, dietary variables, and sedentary lifestyles all have a role in the etiology of diabetes problems. In this special issue, an article titled "Epigenetic Studies Point to DNA Replication/Repair Genesasa Basis for the Heritable Nature of Long Term Complications in Diabetes" was published. They were using a zebrafish diabetes model, A. A. Leontovich etal. investigated the involvement of epigenetic pathways in the persistence of diabetic problems even when euglycemic control is established, a phenomenon known as metabolic memory. They discovered that DNA methylation in or near genes involved in the DNA replication/DNA metabolism process group may play an important role in this process. The Irish Longitudinal Study on Ageing (TILDA), as described by M. L. Tracey et al. in their article "Risk Factors for Macro- and Microvascular Complications among Older Adults with Diagnosed Type 2 Diabetes: Findings from The Irish Longitudinal Study on Ageing," has identified aging, male gender, smoking, low level of physical activity, and high cholesterol as independent predictors of macrovascular complications. In contrast, smoking, hypertension, and DM duration of more than 10 years were found to be risk factors for microvascular complications (Konstantinos Papatheodorou,1 Maciej Banach,2 Michael Edmonds,3 Nikolaos Papanas, 2017).

b) Macrovascular complications-

CVD- CVD is a leading cause of mortality and disability among diabetics. As the number of persons diagnosed with diabetes rises, so, too, will the number of those diagnosed with CVD. Diabetes patients continue to have a two- to fourfold increased risk of hospitalization for significant CVD events and CVD-related clinical procedures as compared to individuals without diabetes. Mortality from CVD Most high-income nations have seen a decrease in CVD death

rates among the general population. Several studies' findings indicate a decrease in CVD-related mortality among diabetics. Between 1988 and 1994 and between 2010 and 2015, there was a 53% relative fall in CVD mortality in the United States, as well as a reduction in the excess risk between diabetic and non-diabetic groups (Harding *et al.*, 2019).

c) Microvascular complications

LEA' s- Because several aetiological pathways are associated with conditions leading to LEAs, LEAs are also an important indicator of the success of preventive care, such as that targeting glycemic control, CVD risk factor management, and screening and treatment of people at high risk of foot complications.

d) Retinopathy-

Diabetic retinopathy is a significant cause of vision loss and blindness in diabetics. It is characterized by a microvascular disorder that may damage each of the peripheral retina, macula, or both. A whole or partial loss of vision may result from vitreous hemorrhage or retinal objectivity. It can be divided into two types in the preceding arrangement: "proliferative diabetic retinopathy" (PDR) and "non-proliferative diabetic retinopathy" (NPDR). In general, NPDR is characterized by a lack of capillary dividers, an increase in microaneurysms and liquid spills, and increased endothelial attachment of leukocytes and monocytes. Diabetic retinopathy is a condition characterized by endothelial cell and pericytes retinal capillary degeneration as a result of ischemia and micro-aneurysm formation. Proangiogenic mediators, particularly vascular endothelial growth factor, are increased in the later stages of the illness, culminating in pathological retinal vessel proliferation (VEGF). Vision loss can be caused by changes in the retinal microvasculature as well as increased retinal vascular leakage. Poor prognosis is closely associated with retinal capillary degeneration or blockage. This is most likely the result of ischemia, based on the following release of antigenic components associated with hypoxia. This advances the illness into a proliferative stage when neovascularization causes visual impedance, known as macula edema, and liquid collecting inside the retina. Several hyperglycemic-mediated mechanisms, including activation of protein kinase C and the polyol pathway, accumulation of advanced glycated end products, and enhanced hexosamine flow, are required for diabetic retinopathy pathogenesis. These pathways promote increased retinal blood flow, increased vascular permeability, activation of numerous growth factor receptors, pericytes loss, capillary basement membrane thickening, and hemorrhage from micro-aneurysms.

e) Neuropathy:

Diabetic neuropathy is the most common and least understood consequence in more than 15% of chronic diabetics. It is a diverse collection of clinical or subclinical symptoms that impact the peripheral nerve system (PNS) as a consequence of diabetes mellitus (DM). It can have varied clinical kinds, routes of pathophysiology, onset, and development. The most prevalent kind of diabetic neuropathy is distal symmetric polyneuropathy. Symptoms vary depending on the

categorization of sensory fibers implicated. Small fiber intervention is the most common early symptom, including pain (acute shooting) and synesthesia (burning). A routine clinical examination and nerve conduction studies, which are used to determine wide fiber efficiency, might cause pain. The most prevalent kind of diabetic neuropathy is distal symmetric polyneuropathy. Symptoms vary depending on the categorization of sensory fibers implicated. Small fiber intervention is the most common early symptom, including pain (acute shooting) and synesthesia (burning). A routine clinical examination and nerve conduction studies, which are used to determine wide fiber efficiency, might cause pain. Electrophysiology and predictive research in neuropathy have been proven to predict not just outcomes such as foot ulceration but also death. Our present view is that both hyperglycemia and risk factors for artery disease, in the long term, establish barrier pathways that damage the micro-vessel endothelium, nerve back cells, and nerve axons (Mezil and Abed, 2021).

Peripheral Artery Disease- One of the most serious diabetic consequences is peripheral artery disease, which is defined as an arterial obstructive excessive illness that reduces arterial blood fluid during rest and advanced activity. Peripheral artery disease has been discovered to be a highly hazardous natural but commonly asymptomatic consequence of diabetes. According to the German Ankle Brachial Index Epidemiological Analysis (GETABI), diabetic individuals aged 65 and up had a 2-fold increased risk of peripheral arterial disease (ABI less than 0.9) and a 2.5-fold increased risk of sporadic claudication. Hyperglycemia, especially hemoglobin glycation, has been found as an independent risk factor for peripheral artery disease. Detecting peripheral artery disease in diabetic people will be tough. Diabetes mellitus is identical to medial calcinosis, which would needlessly elevate the ankle-brachial index despite substantial occlusive artery disease and a fall in true ankle perfusion pressure due to the incomprehensibility of the leg arteries. Causes of PAD in DM patients include vessel wall derangements, which promote arterial inflammation and endothelial cell failure; blood cell abnormalities, including smooth muscle cells and platelets; and hemostasis effects. These vascular abnormalities that lead to atherosclerosis in diabetic patients are frequently present before the disease is recognized, and their incidence increases as blood glucose control and the DM period deteriorate. PAD is caused by vascular wall derangements such as arterial inflammation and endothelial cell dysfunction; blood cell abnormalities such as smooth muscle cells and platelets; and hemostasis causes. These vascular abnormalities that lead to atherosclerosis in diabetic patients are frequently present before the disease is recognized, and their incidence increases as blood glucose control and the DM period deteriorate.

Coronary Artery Disease:

Coronary heart disease is the main cause of morbidity and mortality around the world. Diabetes is linked to a higher risk of coronary heart disease. The seven-year risk of myocardial infarction in patients with no prior history of myocardial infarction is 20.2 percent for diabetics and 3.5 percent for non-diabetics, respectively. Similarly, among individuals with a history of MI, the 7-year MI risk for diabetics and non-diabetics is 45.0 percent and 18.8 percent, respectively.

Coronary heart disease is once again the leading cause of mortality among diabetic patients. Diabetes is associated with any risk factor associated with enhanced atherosclerosis, such as hypertension, dyslipidemia, smoking, and obesity. Microalbuminuria, macroalbuminuria, serum creatinine elevation, platelet impairment, increased inflammation, oxidative stress, endothelial dysfunction, and hypercoagulation are metabolic and hematological risk factors for atherosclerosis. Insulin resistance causes atherothrombosis by increasing levels of the plasminogen inhibitor activator (PAI) and fibrinogen inhibitor (FI).

Cerebrovascular disease:

Complex cerebrovascular problems in diabetic individuals are caused by macrovascular and microvascular abnormalities. In diabetic patients, brain artery abnormalities are classified as ischemic cerebrovascular disease(CVBD's) or hemorrhagic cerebrovascular disease based on pathophysiology and architecture. CVBD's are a group of neurological disorders that affect the blood vessels in the brain. They include ischemic strokes, intracerebral hemorrhagic strokes, aneurysms, arteriovenous malformations, cardiac arrests, and neurological diseases such as functional artery dysfunction and artery dementia, as well as occluded and stenotic carotid arteries.

Another Type of Diabetic Complication-

Diabetic cardiomyopathy:

Diabetic cardiomyopathy is a diseased heart condition that manifests in the absence of other cardiac risk factors, such as coronary artery disease, hypertension, and significant valve dysfunction. In the absence of additional cardiac risk factors, diabetic cardiomyopathy is defined as compromised heart structure and appearance, such as coronary artery disease, hypertension, and severe volvuli disease. Clinical research demonstrates that cardiac insufficiency is widespread in diabetes individuals, ranging from 19 to 26%. The Framingham Heart Study discovered that the risk of heart failure increased with age in both male and female diabetes patients, and this connection was independent of obesity. The pathophysiologic pathways underlying DCM are currently unknown. DCM is caused by a variety of factors, including insulin resistance, microvascular failure, subcellular component deficiencies, metabolic diseases, autonomic cardiac dysfunction, renin-angiotensin system alterations, and maladaptive immunological response.

Diabetic foot:

Diabetic foot ulcers are lacerations that usually occur on the soles of the feet in diabetic patients due to peripheral neuropathy or peripheral arterial disease on all skin layers, necrosis, or inflammation. Approximately 15% to 25% of diabetic patients will develop foot ulcers during their lives, making it the leading cause of non-traumatic subtraction worldwide. Hyperglycemia in the peripheral arteries causes endothelial cell inflammation and smooth cell defects.

Endothelial dysfunction is the most important cause of microcirculation since it results from changes in endothelial cell differentiation, thickening of the vault membrane, decreased nitric oxide release, increased blood viscosity, improvements in microvascular tone, and decreased blood volume (Mezil and Abed, 2021).

Diabetic Nephropathy-

Diabetes causes nephropathy. Diabetic nephropathy (DN) is the leading cause of end-stage renal disease, although its pathophysiology is unknown. Emerging data shows that epigenetic changes and certain microRNAs may have a role in the development of DN by influencing gene expression and modulating intracellular pathways. Overall, histone methylation and other epigenetic changes of DNA throw up a new vista in our knowledge of how DN might evolve when genes and environment interact.

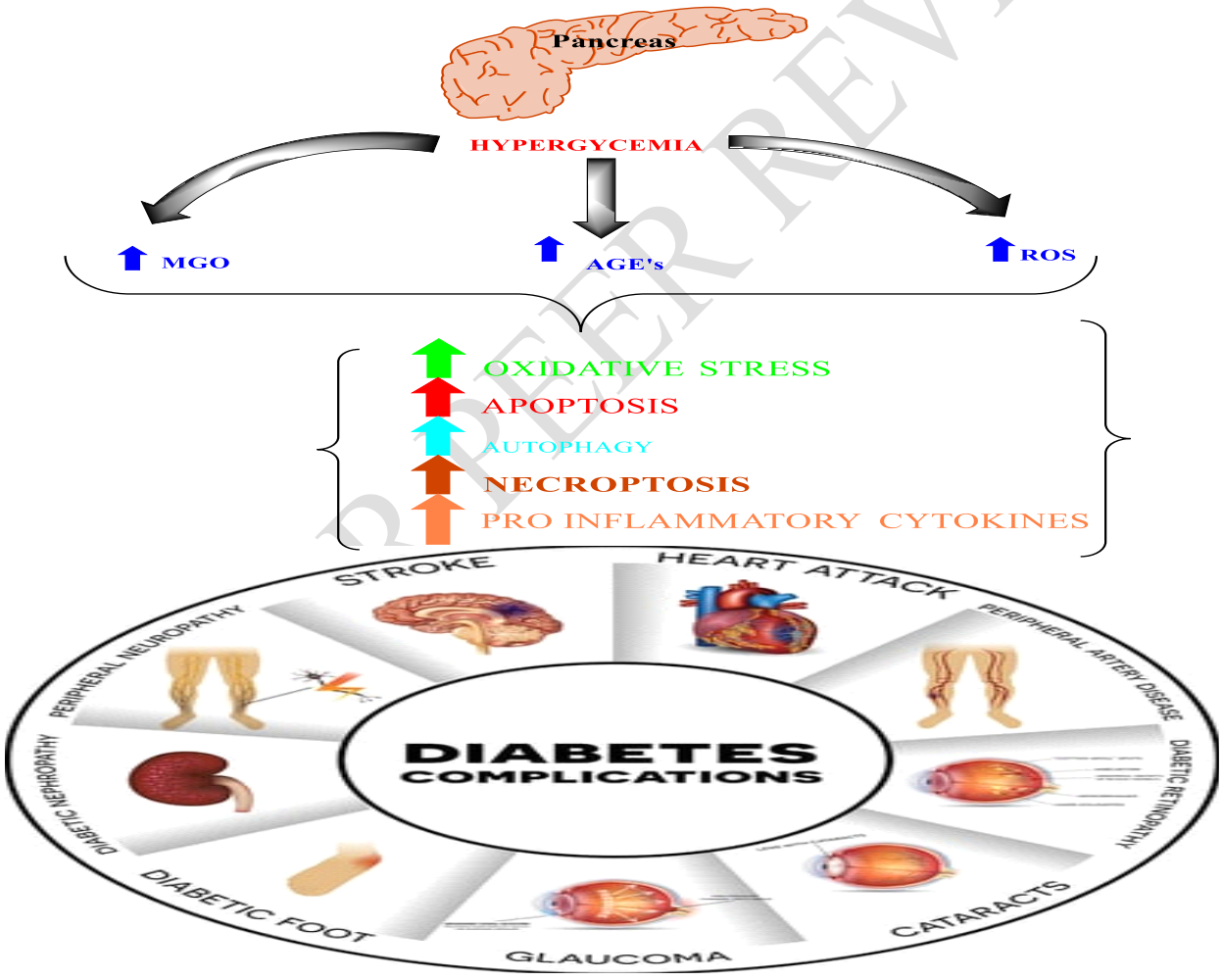

Fig:1 AGEs, ROS, and MGO may promote necroptosis, planned necrosis of inflammatory cells, and apoptosis in diabetes, leading to diabetes-related consequences (retinopathy, age-related macular degeneration, and so on).

MGO = methylglyoxal, AGEs = advanced glycation end products, ROS = reactive oxygen species.

a signalling system crucial in diabetes that, when combined with other metabolic issues, may reduce oxidative stress, pro-inflammatory cytokine secretions, and cellular death. In certain cases, hyperglycemia can cause cellular death, which can lead to diabetes complications and tissue damage. Diabetic problems are thought to be the result of chronic hyperglycemia-induced low-grade inflammation and cellular death. Diabetic problems are thought to be the result of cellular death and chronic hyperglycemia-induced low-grade inflammation.(Volpe *et al*., 2018) It would therefore be appropriate to plan new therapeutic strategies that act upstream of the disease and prevent its progression by reducing neuronal stress and favoring neuroprotection. Furthermore, given the side effects caused by therapeutic agents administered via intraocular injections, there is a need to develop antioxidant and/or anti-inflammatory compounds that can be administered via alternative delivery modalities. Dr. Stephen De Felice developed the word "nutraceutical" in 1989 to describe "a food (or part of a food) that provides medical or health benefits, including disease prevention and/or treatment." Nutraceuticals are strong antioxidants. They may increase the development of antioxidant enzymes, operate as scavengers of reactive oxygen species (ROS), or, as in the case of carotenoids, have singlet oxygen-quenching action. Phenolic chemicals are a major class of secondary metabolites. They have a diverse structure and are responsible for the principal organoleptic aspects of plant-derived foods and drinks, including colour and taste. They also help to improve the nutritional value of fruits and vegetables. Among these chemicals, flavonoids are one of the most common types of plant phenolics. Because of their role in food organoleptic characteristics and human health, a greater knowledge of their structures and biological activities suggests that they have therapeutic potential as well as the ability to forecast and manage food quality. Flavonoids are more accurately referred to as "nutraceuticals" due to their wide range of pharmacological effects in the mammalian body (Lin and Weng, 2006).

Nutraceuticals may also reduce the expression or nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which has anti-inflammatory properties. Nutraceuticals are natural dietary supplements that can be conveniently given, readily available, and reasonably priced. Another advantage of nutraceuticals is that they are unlikely to cause collateral adverse effects such as hypoglycemia, liver harm, or gastrointestinal complaints, which are common with well-known and popular medicines. polyphenols, carotenoids, saponins, and other nutraceuticals (Figure 2), demonstrating how these compounds may mitigate DR degenerative alterations. We focus on how nutraceuticals can help to minimise (i) oxidative stress, (ii) inflammation, (iii) neurodegeneration, and (iv) vascular alterations. Finally, we explore how certain nutraceuticals' limited bioavailability may restrict their utility (Rossino and Casini, 2019).

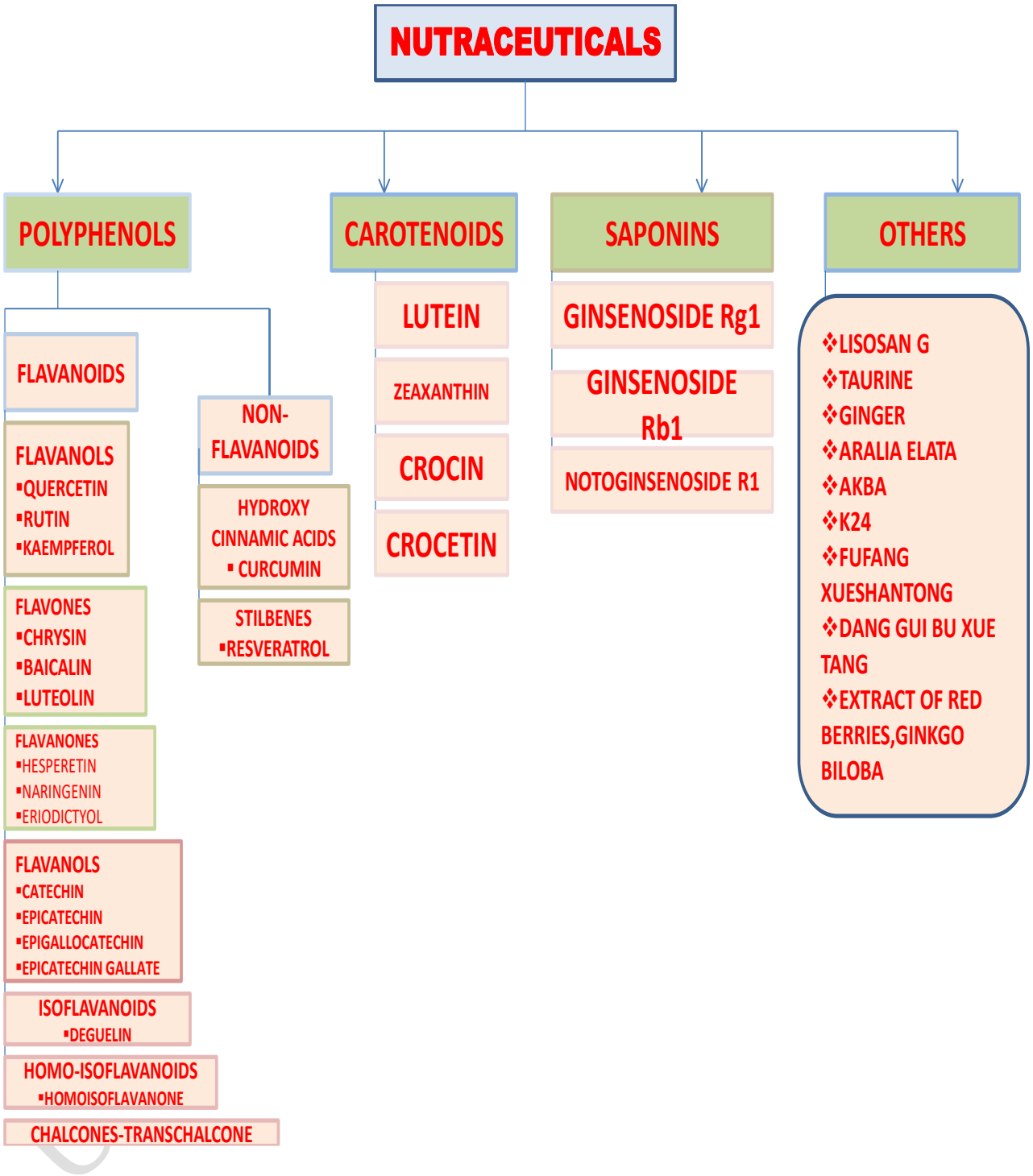

Fig:2 A summary of all the nutraceuticals mentioned in this review. Polyphenols (including flavonoids and non-flavonoids), carotenoids, and saponins are among the substances listed by chemical class. Other compounds classed as "other" are those that do not belong to any of these classifications or are combinations of other chemicals. Acetyl-11-keto-boswellic acid is abbreviated as AKBA.

Polyphenols, carotenoids, saponins, and other natural dietary compounds have been investigated as potential therapeutics or adjuncts to mitigate the retinal oxidative stress associated with diabetic retinopathy (figure 2). Diabetes mellitus (DM) is a chronic metabolic disorder, and the pharmacological properties of *M. oleifera* leaves have been recorded for traditional diabetes treatment. (Kou *et al.*, 2018).

They are present in several fruits, vegetables, herbs, and beverages, and are highly effective in augmenting endogenous antioxidant defenses by direct scavenging action and/or the stimulation of antioxidant enzyme synthesis. Various classes of these pharmaceuticals have been examined in animal models, both in vitro and in vivo. Figure 2 illustrates an overview of the impact of nutraceuticals on oxidative stress in diabetic retinopathy models. Diabetes mellitus is the most frequent noncommunicable disease globally and is increasingly common in emerging countries. The prevalence of disease and its consequences has emerged as a significant worry within our community. We found that numerous patients, especially women and the uneducated, are unaware of these issues and consequently pursue medical care late in the progression of their illness. To manage diabetes effectively and mitigate the onset and progression of complications, it is imperative to educate the community, particularly diabetic patients and their families, to facilitate early diagnosis and appropriate treatment, thereby preventing mortality and long-term complications.(Ullah *et al.*, 2015).

Allium sativum L. (Garlic) and Curcuma longa (Turmeric). Sukandar et al. evaluated the responses of 35 diabetic Indonesians to the investigational treatment, Allium Curcuma capsule (200mg turmeric and 200mg garlic), in comparison to a standard medication, 5mg glibenclamide, with the former yielding a substantial reduction in fasting and 2-hour postprandial blood glucose levels. Throughout the trial, there were no alterations in the patients' blood pressure, hematological profile, hepatic and renal function, or adverse drug interactions. In a separate study, Bitter Melon (Momordica charantia) was examined. The effectiveness of M. charantia (bitter melon) in diabetes management was assessed in a randomized, double-blind, placebo-controlled study. The alteration in HbA1c levels post-therapy was the principal outcome of the study. Unlike previous nonrandomized investigations on the plant, the authors of this study concluded that the consumption of M. charantia had no effect on the HbA1c levels of the diabetic participants. (Salleh *et al.*, 2021).

A multitude of medications has been derived from prototypical molecules present in medicinal flora. Metformin exemplifies an efficacious oral hypoglycemic agent. The design was motivated by the application of Galega officinalis in diabetic treatment. Guanidine, a hypoglycemic agent, is prevalent in Galega officinalis. Due to the excessive toxicity of guanidine for clinical application, the alkyl biguanides synthalin A and synthalin B were introduced as oral antidiabetic agents; however, their use was discontinued once insulin became more readily available. Metformin was developed based on the knowledge gained from guanidine and biguanides. More than 400 traditional plant treatments for diabetes have been documented; however, only a select few have undergone scientific and medical assessment to ascertain their usefulness.(Modak *et*

al., 2007). This study discusses significant Indian medicinal plants with antidiabetic and associated therapeutic effects, along with a list of herbal medications designed for their antidiabetic characteristics. (**Table 1 & 2**).

Table 1. Indian medicinal herbs with anti-diabetic and other health benefits Plant

Name of Plant	**Ayurvedic/common name/herbal mixture**	**Traditional medicine has anti-diabetic and other therapeutic properties.**
Annona squamosa	Sugar apple	Ethanolic leaf extract has hypoglycemic and antihyperglycemic properties, as well as increased plasma insulin levels.
Artemisia pallens	Davana	Hypoglycemic medications can promote peripheral glucose utilisation or limit glucose reabsorption.
Areca catechu	Supari	Hypoglycemic
Beta vulgaris	Chukkander	Increases glucose tolerance in OGTT
Boerhavia diffusa	punarnava	Punarnava An increase in hexokinase activity, a decrease in glucose-6-phosphatase and fructose bisphosphatase activity, an increase in plasma insulin, and an increase in antioxidant activity
Bombax ceiba	Semul	Hypoglycemic
Butea monosperma	palasa	Antihyperglycemic
Camellia sinensis	Tea	Anti-hyperglycemic activity, antioxidant
Capparis decidua	Karir or Pinju	Hypoglycemic, antioxidant, hypolipidaemic
Caesalpinia bonducella	Sagarghota, Fevernut	Hypoglycemic, insulin secretagogue, hypolipidemic Bimb
Coccinia indica	Bimb or Kanturi	Hypoglycemic
Emblica officinalis	Amla, Dhatriphala, a constituent of herbal formulation, “Triphala”	Decreases lipid peroxidation, antioxidant, hypoglycemic constituent
Eugenia uniflora	Pitanga	Hypoglycemic, inhibits lipase activity
Enicostema littorale	krimihrita	Increase hexokinase activity, Decrease glucose 6-phosphatase and fructose 1,6 bisphosphatase activity. Dose dependent hypoglycemic activity
Ficus bengalenesis	Bur	Hypoglycemic, antioxidant
Gymnema sylvestre	Gudmar or Merasingi	Anti hyperglycemic effect, hypolipidemic
Hemidesmus	Anantamul	Anti snake venom activity, anti-inflammatory

indicus		
Hibiscus rosa-sinesis	Gudhal or Jasson	Initiates insulin release from pancreatic beta cells
Ipomoea batatas	Sakkargand	Reduces insulin resistance
Momordica cymbalaria	Kadavanchi	Hypoglycemic, hypolipidemic
Murraya koenigii	Curry patta	Hypoglycemic, increases glycogenesis and decreases gluconeogenesis and glycogenolysis
Musa sapientum	Banana	Antioxidant, Antihyperglycemic
Phaseolus vulgaris	Hulga, white kidney bean	Hypoglycemic, hypolipidemic, inhibit alpha amylase activity, antioxidant. Altered level of insulin receptor and GLUT-4 mRNA in skeletal muscle
Punica granatum	Anar	Antioxidant, anti-hyperglycemic effect
Salacia reticulata	Vairi	inhibitotory activity against sucrase, α-glucosidase inhibitor
Scoparia dulcis	Sweet broomweed	Insulin-secretagogue activity, antihyperlipidemic, hypoglycemic, antioxidant
Swertia chirayita	Chirata	Stimulates insulin release from islets
Syzygium alternifolium	Shahajire	Hypoglycemic and antihyperglycemic
Terminalia belerica	Behada, a constituent of "Triphala"	Antibacterial, hypoglycemic
Terminalia chebula	Hirda	Antibacterial, hypoglycemic
Tinospora crispa		Anti-hyperglycemic, stimulates insulin release from islets
Vinca rosea	Sadabahar	Anti-hyperglycemic
Withania somnifera	Ashvagandha, winter cherry	Hypoglycemic, diuretic and hypocholesterolemic

Table 2 *List of herbal drugs that have been formulated to having anti-diabetic characteristics.*

DRUG	COMPANY	INGREDIENTS
Diabecon	Himalaya	Gymnema sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, Syzygium cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera, Triphala, Commiphora wightii, shilajeet, Momordica charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, Curcuma longa, Rumex maritimus

Diasulin		Cassia auriculata, Coccinia indica, Curcuma longa, Emblica officinalis, Gymnema sylvestre, Momordica charantia, Scoparia dulcis, Syzygium cumini, Tinospora cordifolia, Trigonella foenum graecum
Pancreatic tonic 180 cp	ayurvedic herbal supplement	Pterocarpus marsupium, Gymnema sylvestre, Momordica charantia, Syzygium
Ayurveda alternative Herbal formla to Diabetes:	Chakrapani Ayurveda	Gurmar (Gymnema sylvestre) Karela (Momordica charantia) Pushkarmool (Inula racemosa) Jamun Gutli (Syzygium cumini) Neem (Azadirachta indica) Methika (Trigonella foenum gracecum) Guduchi (Tinospora cordifolia)
Bitter gourd Powder	Garry and Sun natural	Bitter gourd (Momordica charantia)
Dia-care	Admark Herbals Limited	Kadu Sanjeevan Mool; Himej,Jambu beej
Diabetes-Daily Care	Nature's Health Supply	Alpha Lipoic Acid, Cinnamon 4% Extract, Chromax, Vanadium, Fenugreek, 50% extract, Gymnema sylvestre 25% extract Momordica 7% extract, Licorice Root 20% extract
Gurmar powder	Garry and Sun natural Remedies	Gurmar (Gymnema sylvestre)
Epinsulin	Swastik Formulations	vijaysar (Pterocarpus marsupium)
Diabecure	Nature beaute sante	Juglans regia, Berberis vulgaris, Erytherea centaurium, Millefolium, Taraxacum
Diabeta	Ayurvedic cure Ayurvedic	Gymnema sylvestre, Vinca rosea (Periwinkle), Curcuma longa (Turmeric), (Black Babhul), Tinospora cordifolia , Zingiber officinale (Ginger) Syndrex
Syndrex	Plethico Laboretaries	Germinated Fenugreek seed extract

List of the medicinal plants having antidiabetic potential acording to mode of action were presented in Table 3.

Table: 3 List of plants having insulin mimetic or insulin secreatory activity (Modak *et al.*, 2007)**.**

S. No.	Plant botanical name	Common name	Family	Mechanism of action
1	*Abies pindrow*	Morinda	Pinaceae	Insulin secretagogue activity.
2	*Acacia arabica*	Babool	Leguminosae	Release of insulin from pancrease.
3	*Agrimony eupatoria*	Rosaceae	Leaves	Insulin releasing and insulin like activity.
4	*Aloe barbadensis*	Gheequar	Liliaceae	Stimulating synthesis and release of insulin.
5	*Annona squamosa*	Sharifa	Annonaceae	Increased plasma insulin level.
6	*Averrhoa bilimbi*	Bilimbi	Oxalidaceae	Increase serum insulin level.
7	*Bixa orellana*	Annotta	Bixaceae	Increase plasma insulin concentration and increase insulin binding on insulin receptor.
8	*Boerhaavia diffusa*	Punamava	Nyctaginaceae	Increase plasma insulin concentration.
9	*Camellia sinensis*	Green tea	Theaceae	Increase insulin secretion.
10	*Capsicum frutescens*	Mirch	Solanaceae	Increase insulin secretion and reduction of insulin binding on the insulin receptor.
11	*Cinnamomum*	Dalchini	Lauraceae	Elevation in plasma insulin level.

	zeylanicum			
12	*Clausena anisata*	–	Rutaceae	Stimulate secretion of insulin.
13	*Eucalyptus globulus*	Eucalyptus	Myrtaceae	Increase insulin secretion from clonal pancreatic beta line (BRIN-BD 11).
14	*Ficus religiosa*	Peepal	Moraceae	Initiating release of insulin.
15	*Hibiscus rosa*	Gudhal	Malvaceae	Stimulate insulin secretion from beta cells.
16	*Helicteres isora*	Indian screw tree	Sterculiaceae	Decrease plasma triglyceride level and insulin sensitizing activity.
17	*Ipomoea batata*	Shakarkand	Convolvulaceae	Reduce insulin resistance and blood glucose level.
18	*Juniperus communis*	Hauber	Pinaceae	Increase peripheral glucose consumption and induce insulin secretion.
19	*Olea europia*	Olive	Oleaceae	Increase insulin release and increase peripheral uptake of glucose.
20	*Swertia chirayata*	Chirayata	Gentianaceae	Stimulates insulin release from islets.
21	*Scoparia dulcis*	Mithi patti	Scrophulariaceae	Insulin-secretagogue activity.
22	*Tinospora crispa*	Giloe	Menispermaceae	Anti-hyperglycemic, stimulates insulin release from islets.

23	*Urtifca dioica*	Bichhu booti	Urticaceae	Increase insulin secretion.
24	*Vinca rosea*	Sadabahar	Apocynaceae	Beta cell rejuvenation, regeneration and stimulation.
25	*Zingiber officinale*	Adrak	Zingiberaceae	Increase insulin level and decrease fasting glucose level.

Table: 4 In vivo studies of Herbal plants used for the treatment of Diabetes in traditional medicines.

Plant	Part/Route of administration	Method	Animal	Result	Active Constituents	Reference
Acacia arabica	Fruit/oral administration of fruit powder suspension	Aloxan (150 mg/kg s.c.) induced type 1 diabetes	Albino rabbit	Acute hypoglycemic activity in normal rabbit but there was no hypoglycemic action on diabetic animals	—	[12]
Acacia meansii	Bark/polyphenols	High-fat diet induced type 2 diabetes	KKAy mice	↓Body weight, ↓FBS, ↑GLUT4 in skeletal muscle tissue and ↓serum insulin which indicate ↑insulin sensitivity. Improvement of energy expenditure-related mediators: ↑expression PPARα, PPARδ, CPT1, ACO and UCP3; as well as ↑expression of adiponectin and ↓TNF-α in white adipose tissue. Moreover, it suppresses fatty acid synthesis and fat intake in the liver	Robinetinidol and fisetinidol	[13]

Bambusa arundinasia	Dried exudate/oral administration of polyherbal formula	STZ (50 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS, ↑serum insulin, ↓HbA1c, ↓total cholesterol, ↓triglycerides, ↓glucose-6-phosphatase, ↓fructose-1-6-biphophatase and ↑HDL-cholesterol, as well as improvement of pancreatic tissue and Langerhans islets	—	[14]
Bambusa arundinasia	Leaf/oral administration of ethanol extract and fractions	STZ (60 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS via improvement of antioxidant function: ↓LPO, ↑SOD, ↑CAT and ↓GSH in pancreatic tissue. Also regeneration of Langerhans islet and pancreas tissue near to normal, as well as improvement of hepatocyte cells and kidney glomeruli and tubules	β-Sitosterol glucoside and stigmasterol	[15]
Boswellia serrata	Oleo-gum resin/i.p.	Multiple low-dose STZ (40 mg/kg STZ for 5 days) induced type 1 diabetes	BK+/+ wild type mouse	↓Penetration of lymphocytes into pancreatic islets, ↓apoptosis of periinsular cells, ↓G-CSF, ↓GM-CSF, ↓proinflammatory cytokines including: IL-1A, IL-1B, IL-2, IL-6, IFN-γ, TNF-α in the blood, inhibition of atrophy of pancreatic islet tissue and also ↓FBS in diabetic group in comparison with control mice	11-Keto-β-boswellic acid and *O*-acetyl-11-keto-β-boswellic acid	[17]
Bosswellia carterii	Oleo-gum resin/orally	Aloxan (120 mg/kg s.c.) induced type 1 diabetes	Albino rat	↑Body weight, ↓FBS, ↑serum insulin, ↑liver glycogen and also ↓degenerative changes in the β cells of pancreas in comparison with control group	—	[16]

***Coriandrum sativum* L**	Fruit/i.p. administration of ethanol extract	STZ (70 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS, ↑number and activity of pancreatic β cells, ↑insulin release from β cells	—	[18]
***Coriandrum sativum* L**	Fruit/as supplement in diet and drinking water	STZ (200 mg/kg i.p.) induced type 1 diabetes	Heterozygous lean mouse	↓FBS, which was comparable to normal group	—	[19]
Glycyrrhiza glabra	Root/glycyrrhizic acid	High-fat diet induced type 2 diabetes	Sprague-Drawley rat	↓Mean blood glucose, ↑insulin sensitivity, as well as ↓insulin level. ↑Expression of lipoprotein lipase in visceral and subcutaneous adipose tissues, kidney, heart, and abdominal muscle, ↓fatty acid, ↓total cholesterol, ↓LDL cholesterol and also ↓lipid deposition in tissues	Glycyrrhizic acid	[20]
Glycyrrhiza glabra	Root/glycyrrhizin	STZ induced diabetes	Wistar rat	↓FBS, ↑serum insulin level, ↑pancreatic islet cells, ↓HbA1c, ↓cholesterol, ↓triglyceride, improvement of pancreas and kidney tissues, also ↑antioxidant function: SOD, CAT, MDA, and fructosamine	Glycyrrhizin	[21]
Lactuca sativa	Dried exudate/oral administration of polyherbal formula	STZ (50 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS, ↑serum insulin, ↓HbA1c, ↓total cholesterol, ↓triglycerides, ↓glucose-6-phosphatase, ↓fructose-1-6-biphophatase and ↑HDL-cholesterol. Improvement of pancreatic tissue and Langerhans islets	—	[14]
***Myrtus communis* L**	Leaf/oral administration of volatile oil	Alloxan (200 mg/kg i.v.) induced diabetes	New Zealand albino rabbit	↓FBS, ↓triglyceride, ↑CAT, ↑SOD, ↓nitrite-nitrate and ↓MDA in hepatic tissue; but no significant effect on liver activity biomarker	—	[22]

Myrtus communis	—/i.p.	STZ (50 mg/kg i.p.) induced diabetes	Wistar rat	↓FBS, ↓MDA, improve kidney function such as ↑kidney weigh, ↓urine volume, ↓renal MDA, ↓urinary protein excretion, ↑Creatinine clearance, ↑renal GPx and ↓BUN	Myricetin	[24]
***Myrtus communis* L**	Leaf/oral administration of 50% ethanol extract	STZ (150 mg/kg i.p.) induced type 1diabetes, administration of the extract before (1) and after (2) diabetes induction	Mouse	Inhibition of initial hyperglycaemia (1), ↓FBS significantly (2)	—	[23]
Oxalis corniculata	Whole herb/oral administration of aqueous extract	Alloxan (120 mg/kg, i.p.) induced diabetes	Swiss albino mice	↓FBS, ↓triglyceride, ↓LDL, ↓cholesterol, ↑HDL-cholesterol. Also improvement of antioxidant function: ↑SOD, ↑CAT, ↑GPx, ↓LPO, ↑Vit E, ↑Vit C and ↓GSH.	—	[25]
Portulaca oleracea	Aerial part/oral administration of aqueous extract	Genetic induced type 2 diabetes	db/db mice	↓FBS, ↑insulin secretion, improvement of diabetic endothelial dysfunction through ↓triglyceride, ↓LDL-cholesterol, ↑HDL-cholesterol, ↓systolic blood pressure and ↑endothelium relaxant responses (↓vascular tension); as well as suppressing diabetic vascular inflammation: ↓ICAM-1, ↓VCAM-1, ↓MMP-2 and ↓E-selectin in aortic tissue	—	[26]
Portulaca oleracea	Leaf/oral administration of ethanolic extract	STZ (50 mg/kg i.p.) induced type 1 diabetes	Sprague-Dawley rat	↓FBS via ↑antioxidant enzyme: ↑SOD and ↑CAT, ↑GSH-R and ↓LPO in liver and kidney tissue	—	[27]

Punica granatum	Flower/oral administration of aqueous extract	STZ (60 mg/kg i.p.) induced type 1 diabetes	Albino Wistar rat	↓FBS, ↓triglycerides, ↓cholesterol, ↓LDL-cholesterol, ↓VLDL, ↓LPO, ↑HDL-cholesterol, improvement of antioxidant enzymes: ↑GPx, ↑GSH-R, ↑GST, ↑SOD, ↑CAT and ↓GSH	—	[30]
Punica granatum	Flower/oral administration of methanolic extract	Zucker diabetic fatty rats (type 2 diabetes)	Zucker rat	No significant effect on FBS, improve glucose tolerance effect, as well as ↑insulin sensitivity via ↑PPAR-γ mRNA expression and ↑GLUT4 mRNA expression (the insulin-dependent isoform of GLUTs)	Gallic acid	[28]
Punica granatum	Flower/oral administration of methanolic extract	Sucrose loading mice (in vivo α-glucosidase enzyme inhibitory test), glucose loading and normal mice	Mouse	↓Blood glucose in sucrose loading mice, but no effect on blood glucose in glucose loading and normal mice	—	[29]
***Rosa damascena* Mill**	Flower/oral administration of methanolic extract	Maltose loaded normal and STZ (50 mg/kg i.p.) induced type 1 diabetes (in vivo α-glucosidase enzyme inhibitory test)	Wistar rat	Inhibition of hyperglycemia subsequent to high-dose maltose uptake in both normal and diabetic rats, which indicate α-glucosidase activity	—	[30]
Rosa canina	Fruit/oral administration of ethanol extract and various fractions	STZ (55 mg/kg i.p.) induced type 1diabetes	Albino rats	↓FBS with antioxidant function	—	[31]
Vitis vinifera	Seed/oral administration of water-acetone extract	High-fat diet induced type 2 diabetes	C57BL/6J mouse	↑Protective activity from nerve fiber against diabetic peripheral neuropathy	Oligomeric proanthocyanidins	[33]

Vitis vinifera	Seed/oral administration of ethanol extract and its fractions	Genetic induced type 2 diabetes	db/db mice	Whole extract and the ethylacetate/ethanol fraction showed ↓FBS, ↓HbA1c, but no effect on mice body weight	—	[35]
Vitis vinifera	Seed/oral administration of proanthocyanidin extract	STZ (55 mg/kg i.v.) induced type 2 diabetes	Wistar rat	↓FBS, ↓advanced glycation end products, ↓HbA1c, improve kidney function: ↓BUN, ↓creatinine, ↓kidneys/body weight ratio, ↓glomerular hypertrophy, ↓interstitial fibrosis, and also suppression of various protein overexpression ie, ↓GSTM, ↓glutamate carboxypeptidase and ↓β-actin protein expression	Proanthocyanidin	[34]
Vitis vinifera	Seed/oral administration of procyanidin extract	STZ (70 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓Blood glucose level, which was strengthened in accompany with low dose of insulin	Procyanidins	[32]

CONCLUSION AND FUTURE TRENDS OF NATURAL PRODUCTS-

The ancient practice of using plants for medicinal purposes has been carried into modern society as we strive to better understand the pharmacological actions, benefits, and potential risks associated with these botanical remedies. Consequently, herbal medicines continue to be employed in contemporary society for managing and treating diabetes, as well as promoting overall health. Many of the drugs available today are derived from plants, forming a significant part of modern medicine. In this context, various herbs have demonstrated their potential to assist in diabetes management by influencing insulin secretion, insulin sensitivity, glucose regulation, and other factors that contribute to better control of blood sugar levels. Additionally, some herbs have exhibited effectiveness in mitigating cardiovascular complications by reducing triglyceride and cholesterol levels, as well as body mass index (BMI). Due to their perceived natural origin and affordability, herbal medicines are often preferred by patients, either as standalone treatments or as complementary therapies alongside conventional diabetes management. This trend has led to the translation of laboratory research into clinical trials and the development of market-ready herbal formulations. However, the rapid expansion of ethnopharmaceutical approaches for diabetes control highlights the need for standardized testing protocols to assess the quantity and quality of active pharmaceutical ingredients in these herbal products.

Furthermore, these products must undergo rigorous evaluation in human subjects through well-designed clinical trials, ultimately earning certification and approval from regulatory authorities to instill confidence in consumers regarding the safety and efficacy of herbal treatments.

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Details of the AI usage are given below:

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