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A COMPREHENSIVE EVALUATION OF THE HERBAL ROLE IN THE MANAGEMENT OF DIABETIC RETINOPATHY

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Abstract
Diabetic retinopathy, a microvascular consequence of diabetes that causes damage to the eyes, is the factor that is responsible for the majority of the visual impairment that diabetic people experience. Approximately eighty percent of diabetics who have been living with the condition for twenty years or longer will eventually develop diabetic retinopathy. We could minimise the number of new cases by at least 90 percent if we took the appropriate precautions and paid attention to the eyes. In people who have had diabetes for a longer period of time, the risk of developing diabetic retinopathy is higher than in patients who no longer have diabetes. As a result, it is essential to discover a solution to the problem as well as a means to stop it. Due to the fact that the chemical diversity of natural goods has better matches than the diversity of manufactured drugs, natural products are gaining attention in the field of pharmacotherapy. The purpose of this study is present a summary of the possible capabilities of a number of well-known traditional medicines for the treatment and even reversal of the pathogenesis associated with DR. *Aegle ma*rmelos, *Ginkgo biloba*, *Prunella vulgaris*, *Moringa oleifera*, *Lonicera japonica*, *Pueraria lobata*, *Trigonella foenum graceum*, *Origanum majorana L.*, and *Salvia miltiorrhiza* are some of the herbs that are included in this category. Furthermore, it investigates the possible action mechanisms that have been supported by in-vitro, in-vivo, and epidemiological research that has been conducted quite recently.
Keywords: Diabetic retinopathy, Herbs, Diabetes mellitus, Traditional plants

Introduction

One of the most common causes of vision loss that can be attributed to diabetes mellitus (DM) is diabetic retinopathy (DR), which affects persons who are of working age. The clinical features that lead to the diagnosis of diabetic retinopathy include abnormalities in the retinal blood vessels[1]. There are two types of diabetic retinopathy (DR) that might present clinically: proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR). Increased vascular permeability and capillary occlusion are two crucial findings that may be made about the retinal vasculature during the early stage of diabetic retinopathy, also known as NPDR. Fundus photography is now capable of identifying retinal illnesses such as microaneurysms, haemorrhages, and hard exudates, even in patients who may not be suffering any symptoms of these conditions. The progressive DR (PDR) stage, which is the later stage of the disease, is characterised by the presence of neovascularization[2]. Patients may be experiencing tractional retinal detachment or new aberrant arteries leaking into the vitreous (vitreous haemorrhage) at this stage. Both of these conditions have the potential to cause significant vision impairment. In diabetic retinopathy (DR) patients, diabetic macular edoema (DME) is the most common cause of blindness. A condition known as diabetic macular edoema (DME) is characterised by the accumulation of fluid in the macula, which can result in swelling or thickening. This condition occurs when the blood-retinal barrier (BRB) is compromised. Disturbance of the visual image and a reduction in acuity are also potential outcomes of DME, which can occur at any stage of the DR process. There are currently a number of treatment options available for diabetic retinopathy (DR) that concentrate on treating the microvascular issues[1]. These include intravitreal pharmacologic medicines, laser photocoagulation, and

vitreous surgery. Intravitreal injection of anti-VEFG medicines is currently considered the gold standard for treating both early and severe stages of diabetic retinopathy (DR). The traditional laser treatment only serves to maintain the patient's visual acuity. On the other hand, the anti-VEFG treatment has the potential to improve eyesight while producing less adverse effects on the eyes. However, according to the findings of the research conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) (Protocol I), only 29% of diabetic macular edoema (DME) patients who were treated with anti-VEFG medication for a period of two years demonstrated a three-line improvement in best-corrected visual acuity (BCVA)[2]. There is a possibility that the pathogenesis of DR involves other molecular pathways in addition to VEFG, which could explain the inadequate response to anti-VEFG treatment. One of the primary causes of blindness that can be prevented is diabetes mellitus (DM), which is prevalent in both industrialised and underdeveloped countries. Diabetic retinopathy (DR) is associated with a 25-fold increase in the risk of blindness as compared to individuals who do not have diabetes. If you have good control of your blood glucose levels, you can prevent the development of diabetic retinopathy and reduce the amount of visual loss you experience. These technological advancements have resulted in a significant improvement in both the diagnosis accuracy of screening methods and the accessibility of specialist care for diabetic patients. Over the course of the previous three decades, treatment strategies have developed to embrace new methods and techniques, such as pharmacotherapies, early surgical treatments, and laser photocoagulation[3].

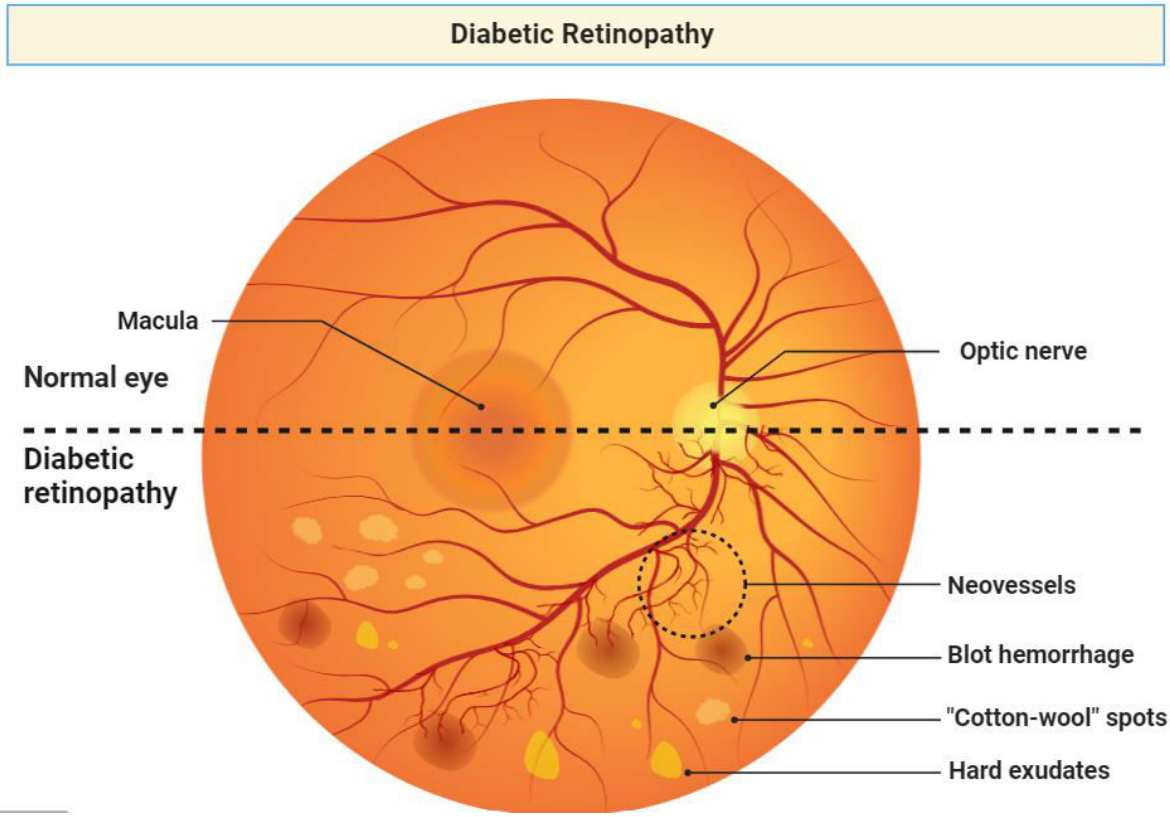

Figure 1: The difference between Normal Eye and Diabetic Retinopathy

Pathophysiology of Diabetic retinopathy

Microangiopathy and capillary obstruction are the fundamental components of the pathogenesis of diabetic retinopathy (DR), which is associated with prolonged bouts of hyperglycemia.

Microvascular leakage and the weakening of the blood-retinal barrier are both caused by the combination of these two factors, which in turn leads to macular oedema, retinal HM, EXs, and oedema among other complications[4]. An increase in VEFG levels is thought to be one of the primary angiogenic factors that contribute to the pathophysiology of DR. In addition, there is a growing body of research suggesting that neurodegeneration is a precursor to the pathophysiology of DR, which may be connected with the development of microvascular abnormalities[5]. In both experimental models of diabetic retinopathy (DR) and in the retinas of diabetic donors, it has been observed that the hallmarks of diabetes-induced neuroglial degeneration, such as reactive gliosis, reduced retinal neuronal function, and neural-cell death, occur prior to the manifestation of overt microangiopathy[6]. The pathophysiologic changes that occur in diabetic retinopathy are associated with chronic hyperglycemia. The physiological and biochemical changes that occur in the retina as a result of persistently increased blood glucose levels are the driving force behind the development of microvascular damage and retinal dysfunction. The blood-retina barrier (BRB) becomes more porous as a consequence of microaneurysms, haemorrhages, and the thickening of the retinal basement membrane that are brought on by chronic hyperglycemia[7]. This allows for leakage from retinal vessels. Enhanced vascular permeability, which in turn leads to capillary occlusion and, ultimately, retinal hypoxia, may be the source of greater levels of vascular endothelial growth factor (VEFG) and the promotion of photodynamic reflex therapy (PDR). The development of fibrovascular membranes and retinal neovascularization are two of the pathological hallmarks of PDR. These changes can eventually lead to vitreous haemorrhage and retinal detachment, which can ultimately result in visual impairment or blindness. DME, also known as diabetic macular edoema, is another prevalent cause of vision loss in diabetic retinopathy (DR). DME is characterised by the disruption of the basal retinal blood flow (BRB) and the accumulation of fluid in the macula, which ultimately results in the proliferation of macular tissue and swelling. DME, which can occur at any stage of the DR process, can cause severe picture distortion or even blindness. This can occur at any time in the operation. Inflammation, micro-vasculopathy, oxidative stress, and neurodegeneration are some of the symptoms that may contribute to the retinal damage that is produced by diabetic retinopathy for some people[8].

Inflammation

The presence of inflammation is necessary during the entirety of the DR process. The identification of inflammatory markers at low dosages exhibits a high degree of reliability in animal models and diabetic individuals. When it comes to diabetic models, leukostasis is associated to endothelial cell loss and BRB damage[9]. In diabetic models, leukostasis is linked to adhesion-molecule-mediated leukocyte-endothelial cell adhesion. Furthermore, investigations conducted on both humans and animals have demonstrated that there is an increase in the amounts of adhesion molecules that are present between leukocytes and endothelial cells[10]. Additionally, chemokines, including as MCP-1, MIP-1α, and MIP-1β, play a role in facilitating the progression of DR. On account of the fact that they attract and activate leukocytes, these chemokines have the potential to make leukostasis worse. Patients diagnosed with DR exhibit an elevated level of inflammatory mediators, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-23 (IL-23), and interleukin-1 beta (IL-1β)[11].

The activation of microglia is a component of the inflammatory response that occurs in DR. When glucose levels are elevated, microglia become active, which leads to an increase in the

expression of TNF-α, IL-6, MCP-1, and VEFG following this activation. In addition, astrocytes and Müller cells are responsible for the production of a multitude of pro-inflammatory chemicals, which is another component of this response that contributes to the accumulation of inflammation in the retina.

Retinal micro-vasculopathy

The fact that DR is classified as a microvascular condition has been known for a considerable amount of time. The retina may be able to adjust to the altered metabolic demands by causing vasodilatation and hemodynamic abnormalities in response to persistent hyperglycemia. This is a possibility[12]. In order for pericytes and endothelial cells to efficiently communicate with one another, hyperglycemia, systemic and ocular hypertension, and DR all play a part in the disruption of the tight connections that are necessary for both of these cell types. Pericyte apoptosis, which is triggered by this disruption, is responsible for the formation of new blood vessels, which occur when vascular endothelial cells multiply in an uncontrolled manner. There is a correlation between the loss of pericytes, which are responsible for maintaining capillary integrity, and the pathophysiology of capillary dilatation as well as the development of microaneurysms[13]. By allowing the newly established vasculature, which is frequently frail and excessively porous, to leak, it is possible for the retina to experience bleeding and edoema. In response to retinal ischemia or hypoxia, hypoxia-inducible factor-1 (HIF-1) is responsible for stimulating the upregulation of vascular endothelial growth factor (VEFG)[14]. The VEFG team is one of the most important participants in the development of PDR and DME. By undergoing the process of phosphorylation, VEFG is able to increase the permeability of the human blood vessels. Moreover, VEFG is responsible for the activation of mitogen-activated protein (MAP), which is responsible for the proliferation of endothelial cells. Patients diagnosed with DR as well as animal models have demonstrated higher levels of VEFG[15].

Oxidative stress

Oxidative stress is responsible for both the increase in the production of pro-inflammatory molecules and the decrease in the effectiveness of antioxidant defence systems found inside cells[16][17]. Oxidative stress occurs when the levels of reactive oxygen species (ROS) reach levels that are considered to be harmful. Under physiological conditions, the antioxidant defence mechanism that organisms use helps to maintain a balance between the creation of reactive oxygen species (ROS) and their removal[18]. This equilibrium is responsible for maintaining the physiological state. Conversely, prolonged hyperglycemia can lead to oxidative stress and a reduction in antioxidant defences, both of which are negative outcomes[19]. The activation of metabolic pathways, the stimulation of mitochondrial oxidative phosphorylation, and the activation of nicotinamide adenine dinucleotide phosphate oxidase are all brought about by hyperglycemia[20]. These three processes are responsible for the increased amounts of reactive oxygen species (ROS). The presence of elevated quantities of reactive oxygen species (ROS) has the potential to create disruptions in the homeostasis of cells and to result in cell dysfunction[21]. Because it contains a high percentage of unsaturated fatty acids and uses a substantial amount of oxygen during the process of glucose metabolism, the retina is an organ that is particularly susceptible to oxidative stress[22]. An increase in the production of reactive oxygen species (ROS) was seen in diabetic mouse models, which was accompanied by a comparable decrease in the activity of antioxidant enzymes[23].

Retinal neurodegeneration

The early stages of diabetic retinopathy (DR) may be marked by retinal neurodegeneration. Studies conducted on both humans and animals have demonstrated an increased expression of pro-apoptotic proteins such as cleaved caspase-3, Bax, and Fas inside the retina[24]. Research has demonstrated that continuous exposure to elevated glucose levels is linked to an increase in mitochondrial fragmentation and cell death in laboratory trials[25]. This association was found to be quite significant[26]. As can be observed in diabetic animal models, the first signs of retinal micro-vasculopathy are the loss of ganglion cells and the development of thinner retinas[27].

Material method

A comprehensive investigation was carried out on the scientific database Pubmed, Scopus, Scielo and Science Direct utilising the keywords Diabetic retinopathy, Herbs and their biological activities.

Herbs role in Diabetic Retinopathy

Aegle marmelos

There are numerous regions in India and Southeast Asia that are home to *A. marmelos*, which is more commonly referred to as Bael[28]. Ex vivo, in vitro, and in vivo tests conducted on rats suggest that it may have the ability to inhibit aldose reductase, the enzyme that is associated with the condition of the lens becoming opaque. It was discovered that the intervention of ethyl acetate extract on α-crystalline, a protein that is water-soluble and extracted from the lenses of rats, resulted in an increase in the chaperone activity of the protein. Benzo[b])-1,4-diazabicyclo[2.2.2]octane, cinnamic acid, and 3,4-dimethoxybenzoic anhydride were the three primary components that were discovered through the process of phytochemical profiling. These compounds, which were isolated from an extract of ethyl acetate, have not yet been researched to determine whether or not they have the power to alleviate DR; nonetheless, it is probable that they do.

Ginkgo biloba

Ginkgo biloba is well-known among practitioners of Chinese traditional medicine for its ability to aid in the treatment of respiratory issues and improve blood circulation abnormalities that are connected with memory loss in Iran[29]. These two medicinal plants, *Ginkgo biloba* and St. John's Wort, both have quercetin as their principal bioactive component[30]. One of the most potent and extensively researched flavonoids found in food, quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one) can be found in a variety of sources, including seeds, barks, flowers, tea, brassica vegetables, onion, berries, nuts, and leaves[31]. It has been proven that quercetin possesses a wide variety of biological activities, some of which include anti-diabetic, anti-carcinogenic, anti-inflammatory, anti-ulcer, anti-allergic, and anti-viral properties. It is able to reduce lipid peroxidation, platelet aggregation, and capillary permeability, among other processes. Because of its powerful antioxidant profile, it modulates antioxidant defence, lowers lipid peroxidation, directly scavenges free radicals, and inhibits xanthine oxidase. All of these effects are brought about by their presence[32]. There are a number of bioactivities that quercetin possesses, some of which include avoiding cataracts, choroidal and retinal angiogenesis, and protecting cells of the retinal pigment epithelium from injury caused by oxidative stress. Research on quercetin-containing green tea and *Moringa oleifera* suggests that quercetin may have a protective function in DR. This is according to the findings of the research. Following treatment with quercetin at doses of 25 and 50 mg/kg body weight, the reduced levels of GSH in the retina of rats that had been induced with diabetes by streptozotocin (STZ) were reversed[33]. There was a considerable reduction in the levels of cytokines in the diabetic retina

of rats that had been intoxicated with STZ by quercetin. When compared to normal retinas, diabetic retinas exhibited a significantly higher rate of ganglion cell mortality and a significantly reduced thickness of the retina when viewed using light microscopy. This influence, on the other hand, was eliminated by the use of quercetin therapy. In the presence of quercetin, it was shown that the expression of NF-κB and caspase-3 was diminished. Additionally, the administration of quercetin was able to ameliorate the elevated expression of glial fibrillary acidic protein P and edoema in the nerve fibre layer and endfeet of the diabetic retina. Additionally, quercetin treatment was able to reduce the expression of aquaporin 4 and diabetes-induced variations in glial fibrillary acidic protein. Because of the impact that quercetin has on the vascular and neuronal components of the diabetic retina, it is possible that it has anti-inflammatory properties[34].

Andrographis paniculata

The main ingredient that is taken from the traditional medicinal herb *Andrographis paniculata* (A. paniculata) is called andrographolide, and it is a diterpenoid lactone that occurs naturally[35]. *A. paniculata* has gained a lot of notoriety due to the fact that it has cooling and detoxifying effects. Over the course of many years, it has been widely used as a treatment for a variety of upper respiratory system infections and sore throats in Asian countries[36]. Androgen has been revealed to possess powerful anti-inflammatory capabilities, as demonstrated by a number of animal models of asthma, pulmonary fibrosis, inflammatory bowel disease, and lung harm caused by cigarette smoke[37]. The effects of andrographolide on STZ-induced DR in C57BL/6 mice were thoroughly examined in recent research conducted by Yu and colleagues. According to the findings obtained from cluster of differentiation-31 retinal immunofluorescence labelling, andrographolide was able to minimise the excessive expansion of the retinal vasculature in mice that had been treated with STZ to have proliferative DR. According to research that investigated permeation using Evans blue, andrographolide was able to inhibit the breakdown of BRB in mice that had been induced with STZ to develop NPDR[38]. Additionally, andrographolide decreased the elevated levels of VEFG in blood and the vitreous cavity, as well as the enhanced mRNA expression of retinal VEFG and its receptors in rats with STZ-induced proliferative DR. This was accomplished by lowering the quantities of VEFG produced by the retina. On the other hand, andrographolide was able to decrease the phosphorylation of p65-NF-κB, as well as the inhibitor of kappa B and the inhibitor of kappa B kinase, in mice that had been induced with STZ to develop NPDR. Furthermore, it was able to suppress the nuclear translocation of early growth response-1 and p65 from NF-κB. Additionally, it was found that andrographolide had a significant impact on the reduction of the mRNA expression of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), serpine1, and tissue factor in the serum and retina, which were all stimulated by STZ. In general, the data suggest that andrographolide exerts a substantial influence on the process of angiogenesis and inflammation of the retina during the initial stages of diabetic retinopathy (DR), which is a key period for signalling linked with VEFG, NF-κB, and early growth response-1 factors. According to the findings of this investigation, andrographolide as a potential therapeutic drug for the treatment of DR has demonstrated promising results[39].

Prunella vulgaris

There are plants that have the ability to heal themselves, such as *P. vulgaris*, which can be found in Northwest Africa, North America, Europe, and Asia. There are a number of bioactive chemicals that can be found in it, including prunellin, caffeic acid ethyl ester, rosmarinic acid, oleanolic acid, ursolic acid, botulinic acid, and 2-hydroxy cinnamic acid. Prunellin, p-hydroxy

cinnamic acid, and caffeic acid ethyl ester are the key compounds that contain the ability to inhibit the function of RLAR. In addition, when compared to the medication aminoguanidine, which is commonly recommended, caffeic acid ethyl ester demonstrates a more potent impact in alleviating diabetic retinopathy through a mechanism that is anti-oxidant and anti-aging. On the basis of these findings, *Prunella vulgaris* might contain active components that could contribute to a reduction in DR. Despite the fact that this is true of many therapeutic plants, additional study that makes use of animal models is necessary in order to understand the precise pathways that are responsible for the development of its anti-aging capabilities[40].

Moringa oleifera

The majority of *M. oleifera* Lam is used by prospects in Pakistan, India, Hawaii, and other African nations. Polyphenolic compounds, which can be found in *M. oleifera*, are responsible for lowering blood glucose levels[41]. They accomplish this by increasing the amount of glucose that is absorbed by the body. In the diabetic retina, it was observed that there was an increase in the expression of TNF-α, IL-1β, VEFG, and PKC-β. Following treatment with *M. olefera*, diabetic retinae exhibited a considerable reduction in the expressions in question. In addition, retinae that were treated with *M. oleifera* exhibited a reduced thickening of the capillary basement membrane and a retinal vasculature that was unaffected[42]. The ability of *M. oleifera* to effectively battle diabetic retinopathy can be attributed to the fact that it possesses anti-oxidant, anti-inflammatory, and anti-angiogenic qualities. Astragalin, which is one of the most important bioactive chemicals found in the plant, has been investigated for its possible anti-diabetic qualities. The researchers found that it decreased the expression of VEFG and alleviated the negative repercussions of high glucose levels, thereby preventing diabetic retinopathy (DR)[43].

Lonicera japonica

Traditional Medicine Lonicera japonica, also known as simply *L. japonica*, is a native Chinese plant that is also known by the name Jin Yin Hua[44]. All of the qualities of *L. japonica*, including its antiviral, anti-inflammatory, antibacterial, antipyretic, and blood fat-reducing capabilities, have been thoroughly documented. One of the components that L. japonica possesses is chlorogenic acid (CGA), among other aspects[45]. Among the most important sources of CGA, which is a polyphenol that is formed by esterifying caffeic and quinic acids, beans, potatoes, apples, and coffee are all included[46]. The antibacterial, anti-inflammatory, antioxidant, and anticarcinogenic properties of CGA have been demonstrated by research of various kinds. A number of ideas have been proposed in order to address the question of how CGA can enhance glucose metabolism. One of the potential effects of CGA is that it inhibits glucose absorption in the small intestine and decreases the amount of glucose that is produced by the liver[47]. Furthermore, because to the antioxidant and metal chelator qualities that it possesses, CGA has the potential to prevent the development of insulin resistance and glucose intolerance inside the body. The role that CGA plays in DR, on the other hand, is not quite evident. The effectiveness of CGA was evaluated in a rat DR model in recent research conducted by Shin and colleagues. Following the administration of STZ to diabetic rats in order to induce DR, this study discovered that CGA had a dose-dependent beneficial effect[48]. The increased levels of VEFG and the decreased levels of tight junctional proteins, including occludin, are effectively blocked by CGA, which does not have an effect on the levels of claudin-5. CGA was also able to reduce the high levels of VEFG that were present in the diabetic retina. The findings of this study lend credence to the utilisation of CGA as a complementary treatment for DR[49][50].

Pueraria lobata

There is a bioactive isoflavonoid called puerarin that can be found in the dried root of *P. lobate*. Through an antioxidant mechanism, purarin is able to prevent the death of neurons and retinal cells, in addition to its many other functions[51]. The activity of superoxide dismutase (SOD) is increased, the generation of radicals is reduced, and the expression of inducible nitric oxide synthase (iNOS) mRNA is not significantly altered. The reduction of oxidative stress is achieved by the inhibition of the formation of the receptor complex and the downregulation of RAGE expression[52]. Furthermore, it prevents the process of apoptosis in retinal pericytes and inhibits the activation of NF-κB and NADPH oxidase by inhibiting the signalling pathways of p47phox and Rac1. Furthermore, it displays anti-angiogenic effects through the reduction of HIF-1α and VEFG mRNA expression. Last but not least, it exhibits its anti-inflammatory capabilities by lowering levels of IL-1β, ICAM, VCAM-1, cell apoptosis, Bax, and Caspase-3. Concurrently, it triggers an increase in the expression of Bcl-2 in mitochondria and inhibits the breakdown of BRB, which ultimately leads to the prevention of DR. The bioactive flavonoid known as genistein has the ability to diminish diabetic retinopathy by inhibiting many processes, including the inhibition of tyrosine kinase, the creation of proinflammatory cytokines, the activation of TNF-α, and the activation of microglial cells[53]. The prevention of retinal edoema is achieved through the inhibition of the interaction between leukocytes and endothelial cells, in addition to the dysfunction of the vascular system. By suppressing the phosphorylation of extracellular signal-regulated kinase (ERK) and p38 MAPK, it is able to accomplish this goal. In addition, this plant includes the isoflavone daidzein, which has been shown to protect against diabetic retinopathy by acting on the PPAR receptor in order to achieve its anti-inflammatory effect. Extraction and research have been conducted on puerarin, which is the primary isoflavone glycoside found in P. lobata. It was found that it inhibits hypoxia-inducible factor-1 mRNA, which in turn modifies the expression of VEFG, and that it eventually protects experimental mice from developing DR. Furthermore, it prevents the development of advanced glycation end products, which is a significant limitation. In order to activate NADPH oxidase and the formation of reactive oxygen species (ROS) that is caused by AGE-BSA, NADPH oxidase requires membrane-integrated cytochrome theta 558, which contains many regulatory subunits. Through the inhibition of the activation of AGE-BSA-induced phosphorylation of p47phox and Rac1, puerarin is able to exert its inhibitory impact. Aside from the fact that it causes hyperglycemia, AGE-BSA also causes an increase in the translocation of NF-κB. Because of this, puerarin therapy is effective in preventing diabetes and complications connected to diabetes by inhibiting the activity of NF-κB that is produced by AGE-BSA. Given all of these factors, it is reasonable to assume that P. lobata is a potential source of flavonoids that are extremely effective against DR. Based on preliminary findings from tests conducted on animals, it appears that this plant has a significant potential to serve as a source of innovative and efficient drugs for the treatment of DR[54].

Trigonella foenum graceum

Every year, plants belonging to the fenugreek family, also known as *Trigonella foenum-graecum*, produce flowers. Additionally, it is a member of the Fabaceae family and possesses three very small leaflets that range in shape from obovate to oblong. The semiarid crop is cultivated in every region of the world, and the seeds of the crop are commonly introduced into South Asian cuisine[55]. Consuming fenugreek seeds, using the leaves as a spice, or even eating the sprouts, microgreens, and fresh leaves as a vegetable are all options for consuming this plant. Sotolon is the molecule that is responsible for the unique sweet aroma that is associated with

fenugreek. The cube-shaped fenugreek seeds, which can range in colour from yellow to amber, are a common component in a wide variety of Indian dishes. These recipes include pickles, daals, vegetable dishes, and spice mixtures such as panch phoron and sambar powder. The process of roasting them brings out their inherent sweetness and flavour while also reducing the harshness of their flavour. Although there has been a limited amount of study conducted on the advantages of fenugreek for digestion, inducing labour, and decreasing blood sugar levels in diabetics, the herb has been used for these purposes for a very long time in complementary and alternative medicine[56]. Researchers discovered that administering fenugreek, also known as Trigonella foenum-graecum Linn., to rats that had been genetically modified to develop diabetic retinopathy reduced the development of the illness in the rats. When retinas are treated with fenugreek, there is a considerable reduction in the amount of inflammation as well as angiogenic markers. The stress that is placed on the retina can still be managed. A reduction in the thickness of the capillary basement membrane was observed in rats that were administered fenugreek, as demonstrated by the findings. Recently, a group of researchers lead by Gupta investigated the effects of fenugreek on diabetic complications in rats that had been engineered to develop diabetes through the use of STZ. The expression of retinal inflammatory (IL-1β and TNF-α) and angiogenic (VEFG and PKC-β) molecular markers was much higher in diabetic retinas compared to normal retinas. This was observed after the injection of STZ into Wistar rats. Fenugreek, administered at doses of 100 and 200 mg/kg body weight, was able to inhibit the production of angiogenic and inflammatory molecular markers upon completion of a treatment period of twenty-four weeks. In addition, the diabetic retina's levels of catalase and superoxide dismutase were brought back to normal by the administration of fenugreek. Fluorescein angiograms and fundus pictures of diabetic retinae were able to detect the presence of vascular leakage in the posterior retina. On the other hand, retinae that were treated with fenugreek exhibited the opposite effect. In diabetic retinae that had been caused by STZ, fenugreek was likewise able to lower the thickness of the basement membrane. Therefore, fenugreek has the ability to protect the retinas of diabetics from the deterioration that diabetes causes. It has also been reported that a novel insulinotropic compound known as 4-hydroxyisoleucine has been characterised. The extraction and purification of this amino acid was accomplished by the utilisation of fenugreek seeds, which, according to conventional medical practices, has anti-diabetic properties. Isolated Langerhans islets from both rats and humans are directly influenced by 4-hydroxyisoleucine, which has the ability to enhance glucose-induced insulin release within the concentration range of 100 μmol/l to 1 mmol/l. Although 4-hydroxyisoleucine did not have any effect at low (3 mmol/l) or baseline (5 mmol/l) glucose concentrations, it did increase insulin secretion in response to supranormal (6.6-16.7 mmol/l) glucose concentrations, which demonstrated that its stimulating action was dependent on glucose levels.A substance known as 444-hydroxy leuciene has been shown to increase the amount of insulin that is secreted by pancreatic islet cells in response to glucose stimulation[57].

Origanum majorana L.

Throughout the region of the Mediterranean and Southern Europe, the perennial herb known as *O. majorana* can be found growing naturally. In the eyes of the ancient Greeks, it was a symbol of love and happiness. In addition to having anti-oxidant and anti-aging effects, extracts from O. majorana also contain anti-glication features. The reduction of sugars, amadori adducts, and dicarbonyl intermediates, as well as their conversion to AGE, is an essential step in the process of preventing the creation of these specific molecules, and it also contributes to the process[58]. In order to determine whether or if the triterpenoids ursolic acid (UA) and oleanolic acid (OA),

which are two of the plant's key bioactive components, have the ability to diminish DR due to their antiglycative characteristics, research has been conducted on these two compounds. By increasing renal glyoxalase I activity, decreasing renal methylglyoxal levels, and increasing renal GLI mRNA expression, OL has the capacity to decrease renal sorbitol dehydrogenase activity[59]. This is because both of these factors have the ability to enhance renal GLI mRNA expression. In addition, research conducted on animals to investigate the protective effects and mechanisms of UA has demonstrated that it has the ability to hasten the recovery process following DR, reduce the expression of VEFG, COX-2, and MMP-2 in renal tissue, and block vascularization. All of the research suggests that taking supplements containing UA or OA may help minimise the symptoms of direct reaction (DR)[60].

Salvia miltiorrhiza

The plant *Salvia miltiorrhiza*, which is sometimes referred to as Danshen in Chinese, is frequently utilised in traditional Chinese herbal medicine applications. Compound Danshen Dripping Pill (CDDP), a Chinese herbal medicine product that contains danshen, has been utilised for the treatment of cardiovascular issues because of its effectiveness[61]. Danshen, notoginseng, and borneol are the three herbs that are included in this pill. Traditional Chinese medicine has a long history of being used for treating a wide variety of illnesses. When it comes to pain and blood circulation, CDDP has been proven to be beneficial by certain individuals. The most common reason for diabetic retinopathy (DR) in Chinese patients is blood stasis, which leads to the destruction of the eye's collateral veins. Because of this, CDDP has been demonstrated to improve the symptoms of DR in a number of clinical trials and experimental investigations that have been conducted with patients who have DR. A large-scale clinical experiment was conducted by Lian and colleagues in a recent study[62]. The purpose of the experiment was to evaluate the effectiveness and safety of CDDP in a total of 223 individuals who were diagnosed with NPDR. Over the duration of the trial that lasted for twenty-four weeks, participants were randomly assigned to one of four groups: placebo, low-dose (270 mg), mid-dose (540 mg), or high-dose (810 mg) of herbal medicine. The data that was acquired via fluorescence fundus angiography after 24 weeks revealed that the percentage of persons who were assessed as "excellent" or "effective" was much higher in the groups that were given mid- or high-dose CDDP (77% and 74%, respectively) in comparison to the group that was given a placebo (28%). When compared to the placebo group, the percentage of participants who regarded the treatment as "excellent" or "effective" was much higher in the groups that were given a mid- or high-dose of CDDP (42% and 59%, respectively) than in the placebo group (11%). It was determined that there were no cases of adverse events that were regarded to be clinically significant. This clinical trial demonstrates that a Chinese herbal medication that contains danshen is both safe and helpful for people suffering from Duchenne muscular dystrophy (DR)[63].

Conclusion

In many regions of the world, diabetic retinopathy is the most common cause of blindness that can occur without medical intervention. The results of a recent study have demonstrated that hyperglycemia is the primary contributor to the development of diabetic retinopathy (DR) and the acceleration of its progression. Hyperglycemia causes damage to the capillaries of the retina through a number of different ways. These mechanisms include the activation of protein kinase C, the amplification of non-enzymatic glycation, the enlargement of the polyol pathway, and the formation of reactive oxygen species (ROS). The creation of novel therapy alternatives will be made possible by conducting additional research on the specific pathological abnormalities that

are associated with DR. The prevention of disease, the improvement of mental health, the treatment of non-communicable diseases, and the enhancement of the quality of life for the aged and those with chronic ailments are some of the areas in which TM has demonstrated its potential to be effective. Research conducted in clinical and preclinical settings suggests that traditional medicinal plants may include innovative oral hypoglycemic medicines. This is the conclusion drawn from researchers. This could be a reasonable option in view of the current situation in the pharmaceutical sector, which is characterised by a limited supply and rapidly increasing prices. In this field of research, the objective is to gain a better understanding of how medicinal plants could be utilised to treat eye diseases. This will be accomplished by locating and analysing particular bioactive components or isolated compounds that have the potential to enhance vision or minimise damage to retinal cells. This is mostly due to the fact that synthetic retinoprotective drugs and therapies are extremely expensive and are only available in restricted quantities. Natural commodities should be given priority in the attempt to restore human health since they are abundant, inexpensive, and easily accessible to a large number of people. This is due to the fact that they contain a wide variety of active substances that are not only efficient but also diverse. People have the ability to improve their overall health and reduce their risk of getting diabetes and associated consequences, such as diabetes-related rheumatoid arthritis, by including medicinal herbs into their daily meals.

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