Role of Herbals in Treatment of Diabetes Mellitus: A Scientific Review

Madhur Kant¹, Dr. Rakesh Kumar Meel², Dr. Bhanu P. S. Sagar³, Dr. Amrita Singh⁴, Snehil Singh⁵

¹Renu Mahesh Pharmacy College, Sitapur, Lucknow, Uttar Pradesh, India.
²Dr. Rakesh Kumar Meel, School of Pharmacy, Glocal University, Saharanpur, UP.
³IEC Department of Pharmacy, IEC College of Engineering & Technology, IEC Group of Institutions, Greater Noida, Gautam Budha Nagar, Uttar Pradesh, India.

Diabetes Mellitus: General Introduction

Seki et al., 2004, have reported that Diabetes mellitus (DM) is a group of metabolic disorder which is affecting all age groups and having devastating complications. DM result from a defect in insulin secretion (pancreas not producing enough insulin), insulin action (cells not responding properly to the insulin produced), or both. (Joseph et al., 2011)

Senthilkumar and Subramanian (2007), illustrated that oxidative stress / oxidative damage is a pathogenic factor in development of diabetic complications. DM chronic complications include hyperglycemia, hyperlipidemia, oxidative stress, retinopathy, nephropathy, neuropathy, peripheral atherosclerotic vascular diseases and atherosclerotic coronary artery disease. (Wang et al., 2013)

Hegde and Jaisal (2014), Diabetes mellitus has been characterized as genetically based predisposition and dietary indiscretion.

Prevalence of Diabetes mellitus

Rahelic (2016) had reported that diabetes affects 5-7% of the world’s population and consistently growing across the globe (415 million in 2015 to 642 million by 2040). International Diabetes Federation (IDF) reported that estimated diabetic population has soared to 366 million and this number to increase to 552 million diabetic patients by 2030. India has world’s largest diabetes population (50.8 million) followed by China with 43.2 million. Type-2 DM (T2DM) expanded over 70% in developing countries. (Rawal et al., 2012)

Epidemiology of Diabetes Mellitus

WHO (2016), IDF found that rural prevalence of diabetes in 2017 was 146 million people whereas urban prevalence of diabetes in 2017 was 279. In 2045, DM will raise to 156 million in rural and 473 million in urban.

Symptoms of Diabetes Mellitus

Symptoms include excessive thirst, tiredness, polyurea, fatigue, weight loss, polyphagia, nausea, headache, mood swing, blurr vision, balanitis, polydipsia, pruritus vulvae, retinopathy, nephropathy etc.

Classification of Diabetes mellitus (DM) (Porth, 2005)

There are two major types of DM:

(i) Type I - Insulin-dependent DM (IDDM)
   Sub-classified into 2 types:
   a) Type I (A) : Autoimmune DM.
   b) Type I (B) : Idiopathic DM.

(ii) Type II – Non-insulin-dependent DM (NIDDM)

Type-I DM (Cohn and Roth, 1996; Bonk, 1999)

Autoimmune disorder (pancreas produce no insulin, absolute insulin deficiency)

- Type I(A) DM: Destruction of beta cells.
Type 1(B) DM: Insulin deficiency leads to ketosis.

Type-II DM (Walsh, 2002)

- Walsh, (2002), T2DM is maturity-onset diabetes (β cell deficiency; down regulation of insulin; obese and non-obese type; 80% cases; NDDM).
- De Fronzo, (1997), T2DM show poor insulin secretion and insulin resistance;
- Zimmet, (2001), T2DM can be treated by controlled diet and anti-diabetics.

Gestational Diabetes mellitus

Impaired Glucose Tolerance & Fasting Glucose (Drucker et al., 1998)

Difference between different Types of Diabetes Mellitus

WHO characterization of diabetes depends upon certain clinical qualities. American diabetes association (2019) stated that other kinds of diabetes are also observed due to different causes, e.g., monogenic diabetes disorders (neonatal diabetes); medication or substance prompted diabetes (glucocorticoid use in the treatment of HIV/AIDS / after organ transplantation).

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
<th>Symptoms</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type - 1 DM or (T1DM/ IDDM)</td>
<td>Cell mediated autoimmune destruction</td>
<td>Polydipsia; Polyuria; Polyphagia; Weight loss; Fatigue; Blurred vision</td>
<td>Mostly affects juveniles and adults</td>
</tr>
<tr>
<td>Type - 2 DM or (T2DM / NIDDM)</td>
<td>Insulin resistance occurs (decrease the capability of insulin to excite glucose uptake in peripheral tissues), β cell do not secrete insulin adequately</td>
<td>Hyperglycemia. Loss of glucose in urine; Weight loss; Fatigue; Blurred vision; Headache</td>
<td>Mostly occurs in adults</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>Glucose prejudice with a beginning or first analysis of pregnancy (danger of creating T2DM in both mother / kid.)</td>
<td>Impaired glucose tolerance. Hyperglycemia.</td>
<td>Occurs in pregnant women</td>
</tr>
</tbody>
</table>

Pathogenesis of Diabetes Mellitus

Type-1 DM (T1DM / IDDM) Pathogenesis

Al Homsi and Lukic (1992) have summarised that T1DM is related with annihilation of insulin conveying pancreatic β-cells (Figure 1-2) and also clarified that T1DM as an immune system malady:

(i) Occurrence of immuno-able and adornment cells in pancreatic islets.
(ii) Sickness with the class II (inulnerable reaction).
(iii) Islet cell explicit auto antibodies
(iv) Modification of T cell mediated immuneregulation.
(v) Commitment of monokines and TH1 cells conveying interleukins in sickness.
(vi) Retort to immunotherapy.
Pathophysiology Mechanism of IDDM

- Absolute lack of insulin
- β cell mass reduction

Mechanisms for destruction of islet cells

- Acute autoimmunity
- Environmental insult
- Genetic susceptibility

Figure 1: Pathogenesis/pathophysiology of DM.

Pathogenesis of Type-2 DM / NIDDM

NIDDM has a more unmistakable inherited bond than T1DM, the pathogenesis of NIDDM is depicted by weakened insulin emanation and insulin obstruction as showed up in Figure 3-4.
Figure 3: Pathogenesis of NIDDM (Ozougwu et al., 2013)

<table>
<thead>
<tr>
<th>Pathophysiology Mechanism of NIDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insulin resistance</td>
</tr>
<tr>
<td>• Insulin secretion Impairment</td>
</tr>
</tbody>
</table>

Mechanisms for development of NIDDM

• Defect in Insulin receptor
• Defect in β-cell function
• Combination of both

Figure 4: Mechanism of Pathogenesis of NIDDM.

**Impaired Insulin Secretion**

Dysfunction of β-cells is induced because of defects in gene level e.g. GLUT-2 gene, mitochondrial gene, insulin gene and glucokinase gene.

**Insulin Resistance**

Environmental and genetic factors predispose to Insulin resistance (hereditary variables include insulin receptor, quality polymorphism in IRS-1 insulin receptor, β3 adrenergic receptor quality and the uncoupling protein (UCP) quality).

**Complication of Diabetes Mellitus**

- Microvascular disease; Keto-acidosis; coma;
- Microvascular: retinopathy; nephropathy; neuropathy (Andy, 2014)
- Myocardial infarction; strokes (Walsh, 2002)

**Risk Factors of Diabetes Mellitus**

(i). Non-modifiable: Age; Family history
(ii) Modifiable: Obesity; stressful life; Alcohol use; Tobacco use; Physical immobility; Trans fat and high dietary glycemic load (unhealthy diet)

Besides, other diabetes factors include standard of living like urban / western, history of gestational diabetes, ancestors narration of NIDDM, aging and polycystic ovarian syndrome. (Walia et al., 2014).

**Diagnosis of Diabetes**
There are three diagnostic tests for diabetes mellitus:

- Fasting Plasma Glucose (FPG) (Ronald et al., 2013)
- Random Plasma Test (Anees et al., 2013)
- Oral Glucose Tolerance Test (Harikumar et al., 2015)

**Screening Models for Anti-diabetic Drugs:**

(i) **IDDM Screening methods**
- Chemically induced diabetes
- Surgically induced diabetes

(ii) **NIDDM Screening methods**
- In-vitro assay of insulin on adipocyte
- Isolated pancreas of rat [in-vitro]
- Insulin receptor binding assay
- Normoglycemic animal model (glucose)
- Chemically induced diabetes (STZ / Alloxan)
- Glucose uptake by isolated diaphragm from mice/rat

**Alloxan and Streptozotocin produced diabetes**

![Diagram](image)

Figure 5: Alloxan and Streptozotocin produced DM.

**Alloxan induced DM (150 / 160/170 mg/kg by i.p. / i.v. in 5% saline)**

Production of free radicals; irreversible diabetes; necrosis / death of β-cells;

**Disadvantage**

- High mortality; Ketosis in animals; Diabetes induced- reversible
- Guinea pig are resistant to its effect
**Alloxan Induced DM**

**Mechanism of action**

- Free oxygen radical
- Free radical β-cell death
- Reaction with -SH group of protein
- Cell necrosis

Figure 6: Mechanism of Action of Alloxan Induced DM.

**Mechanism of Action of Streptozotocin (STZ) induced DM**

(100 mg/kg; 07 days i.p. in 0.1M citrate buffer)

**Streptozotocin (STZ) induced DM**

- Broad spectrum antibiotic produced from streptomyces acromogens
- Induce DM in almost all species
- Cyclosporine-A enhance STZ-diabetogenic efficacy

Figure 7: STZ induced DM

**STZ induced DM**

**Mechanism of action**

- Methylation
- Free radical generation
- Nitric oxide production

Figure 8: Mechanism of Action of STZ induced DM.
STZ induced DM (100 mg/kg; 07 days i.p. in 0.1M citrate buffer)

Advantages over Alloxan
- Greater selectivity towards β-cell
- Lower mortality rate
- Longer-irreversible DM induction

Disadvantages
- Rabbit resistant to diabetogenic action

Figure 9: Advantage of STZ over Alloxan.

How is DM treated?

IDDM needs insulin treatment (Felig et al., 1995).
NIDDM treatment with medicines and controlled diet (Rosac et al., 2002)

Management of Diabetes Mellitus (Inzucchi et al., 2015)

Hypoglycemic agents are used for the treatment include (Nathan et al., 2009):

(i) dipeptidyl peptidase 4 inhibitors (sitagliptin);
(ii) biguanide (metformin);
(iii) glucosidase inhibitors (acarbose);
(iv) sulphonylurea (glibenclamide);

Figure 10: Process of Drug Research and Development.
Disadvantages of Allopathic Anti-diabetic Drugs (Hassan et al., 2014)

Side effects / unwanted issue, caused by anti-diabetics are as follows:

(i) Sulfonylureas: Stomach upset, hypoglycemia, skin rash, weight gain;
(ii) Biguanides/Metformin: kidney complications, GIT disturbances, dizziness;
(iii) Alpha-glucosidase inhibitors: GIT disturbances, diarrhea and bloating;
(iv) Thiazolidinediones: Obesity, anaemia, liver disease, swelling of legs;
(v) Saxagliptin (DPP-4 inhibitors): Pancreatitis, hepatitis, kidney impairment.
(vi) Saroglitazar (PPAR agonists): Gastritis and pyrexia (Osadebe et al., 2014)

Medicinal Plants as Anti-diabetic Drugs (Mukherjee et al., 2009)

There are more than 500 anti-diabetic medicinal plants which include Momordica charantia, Gymnema sylvestre, Trigonella foenum, Syzygium cumini, Curcuma longa, Phyllanthus emblica, Tinospora cordifolia, Berberis aristata, Aegle marmelos, Pterocarpus marsupium, Glycyrrhiza glabra, Liriope spicata, Azadirachta indica, Commiphora wighti, Ficus glomerata, Terminalia chebula, Asparagus racemosus, Tribulus terrestris, Piper nigrum, Picrorrhiza kurroa, etc.

Role of Natural Products in Diabetes

Hanhideva et al., 2010 illustrated that phytochemicals like anthocyanins and polyphenols reduce the risk T2DM as they activate insulin receptors and stimulate insulin secretion from the pancreas. (Cooper et al., 2012)

Advantages of Herbal Medicine (Debjit et al., 2009; Arun et al., 2012)

(i) The low cost of the herbal products make it economically feasible;
(ii) Easy availability of herbal medicine products for consumption;
(iii) Herbal medicines are relatively harmless, digest easily, with minimum or no side effects and safe. (Wickramasinghe, 2006; De Smet et al., 1997)

Indian Anti-diabetic Herbal medicine

Rao et al., 2010, revealed that in India natural medicines / herbal drugs (unconventional) are used to treat / prevent / cure diabetes. (Table 2)

Table 2: Anti-diabetic herbal formulations.

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cogent DB</td>
<td>Azadirachta indica, Curcuma longa, Phyllanthus emblica, Terminalia chebula, Syzygium cumini, Terminalia belarica,</td>
</tr>
<tr>
<td>Diabon</td>
<td>Ficus racemosus, Phyllanthus emblica, Momordica charantia, Piper cubeba, Styax officinalis, Terminalia belarica, Terminalia chebula,</td>
</tr>
<tr>
<td>Diabaquit</td>
<td>Aegle marmelos, Azadirachta indica, Curcuma longa, Gymnema sylvestre, Momordica charantia, Tinospora cordifolia, Phyllanthus emblica, Trigonella foenumgraecum, Syzygium cumini.</td>
</tr>
<tr>
<td>Dibex</td>
<td>Momordica charantia, Pterocarpus marsupium.</td>
</tr>
<tr>
<td>Madhuhari</td>
<td>Acacia Arabica, Aegle marmelos, Azadirachta indica, Momordica charantia, Phyllanthus emblica, Styax officinalis, Tinospora cordifolia, Trivang bhasma.</td>
</tr>
<tr>
<td>Madhu-</td>
<td>Acacia catechu, Abhrak bhasma, Aegle marmelos, Azadirachta indica, Cinnamomum, Curcuma longa, Emblica officinalis, Ficus racemosus, Gymnema sylvestre, Momordica charantia, Picrorrhiza kurroa, Plumbago</td>
</tr>
<tr>
<td>mehhari</td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of Action of Herbal Anti-diabetics

- Adrenomimeticism,
- Stimulation of insulin secretion
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells
- Reduction in insulin resistance
- Inhibition of β-galactocidase and α-glucocidase
- Increasing the size and number of cells in the islets of Langerhans
- Cortisol lowering activities
- Inhibition of alpha-amylase

Diabetic Retinopathy - The Ocular Complication of Diabetes mellitus

Lee et al., 2015, Diabetic retinopathy (DR) is a form of retinal microangiopathy that occurs as a result of long-term Diabetes mellitus (DM). Patients with Diabetes mellitus typically suffer from DR as a progression of the disease that may be due to initiation and dysregulation of pathways like the polyol, hexosamine, the AGE/RAGE, and the PKC pathway, which all have negative impacts on eye health and vision. DR has become a major global cause of blindness in the population. International Diabetes Federation estimates that the number of diabetic patients may increase to 700 million cases by 2045, and this may consequently lead to a great number of patients with very serious disorders in the visual system. According to statistics, in 2017, the visual dysfunction caused by diabetes affected 2.6 million individuals around the world, accounting for 2.6% of cases of vision loss on the global scale. (Kusuhara et al., 2018)

Gürler et al., 2000, at present, the prevalence of diabetic eye complications such as diabetic cataract and diabetic retinopathy, the leading causes of an acquired blindness, is increasing due to the survival of diabetic patients. Oxidative stress contributes an important role in the pathophysiology of diabetic cataract and diabetic retinopathy. (Madsen et al., 2008)
Figure 11: Pathway abnormalities due to hyperglycemia which leads to ROS generation and oxidative stress contributes to diabetic retinopathy.

Kowluru, (2003), found that more than 536 million people were diagnosed with diabetes in 2021, and this will reach 783 million in 2045. DR is the leading cause of preventable vision-loss in the working population and affects one-third of diabetic patients and 90% of patients will have DR within 25 years of diagnosis. It is a complex, multifactorial neurovascular disease. (Resnikoff et al., 2004)

Klettner and Roider (2009), oxidative stress can induce cataract and retinopathy by numerous pathways including the activation of polyol pathway, vascular endothelial growth factor (VEGF), and mitogen-activated protein kinase (MAPK) Based on the crucial roles of oxidative stress mentioned earlier, the possibility to prevent or to improve diabetic cataract and diabetic retinopathy by antioxidant has been raised. (Kowluru and Chan, 2007)

Cheung et al., 2010, illustrated the whole process of DR includes the following key events: loss of retinal capillary pericytes, basement membrane thickening, loss of endothelial barrier function, and breakdown of the blood retinal barrier, which will lead to the ischemia of retina. Further, retinal ischemia will result in the elevation of vascular endothelial growth factor (VEGF), which contributes to neovascularization and fibrosis which is the hallmark of proliferative stage of DR. (Kohner, 1993; Infeld and O'Shea, 1998)
DR is one of the potentially important microvascular consequences of diabetes mellitus. The participation of various factors, the regulation of numerous genes, and the progression of numerous stages are characteristics of the complicated process that underpins the pathogenic processes. Numerous interrelated pathways and other mechanisms have an impact on the development and progression of DR like the polyol pathway, Nrf2, ALR2, and ROS. Both compounds curcumin and β-glucogallin are capable of inhibiting the included mechanism which give rise to diabetic retinopathy.

Being a complex multifactorial disorder the management of Diabetic Retinopathy is also not fixed. It requires multidisciplinary approach individualized according to severity of the disease.

The primary preventive measure is good glycaemic control, and it is beneficial in reducing the incidence and progression of DR. Progression of Retinopathy in Diabetes can be reduced by 25% in the case of Diabetes Type I and 39% in the case of Type II with each 10% decrease in the level of glycated haemoglobin. There is no proper / perfect treatment available for Diabetic Retinopathy, prevention is the best approach to reduce blindness.

Classification of Diabetic Retinopathy

Diabetic Retinopathy classified into two stages based on the severity and the progression of the diseases.

(i) **Non-Proliferative Diabetic Retinopathy**

Non-Proliferative Diabetic Retinopathy (NPDR) the first clinical signs of DR. One of the earliest clinically detectable sign of diabetic retinopathy include the appearance of small and local lesions of microaneurysms, small retinal haemorrhage and distortions called Intra Retinal Microvascular Abnormalities (IRMA).

Moderate NPDR is characterised by extensive Intra Retinal haemorrhage and a poorly perfused retina within which venous vascular wall may distend. Severe NPDR includes blockage of significant no of small blood vessels in the retina. As a result, the retina becomes deprived of oxygen. Vascular endothelial growth factor (VEGF) and protein kinase C beta (PKC-β) are highly responsible for this condition.

(ii) **Proliferative Diabetic Retinopathy**.

Diabetic Retinopathy further classified into Mild, Moderate and Severe.

**Mechanisms of Diabetic Retinopathy:**

Figure 12: Microvascular complications of diabetic retinopathy.
(i) Hyperglycaemia
(ii) Advanced Glycation Endproducts
(iii) Polyol Pathway
(iv) Oxidative Stress in Diabetic Retina

Diabetes and Hyperglycaemia cause oxidative stress in the Retina and may play a pivotal role in the development of diabetic retinopathy by damaging the retinal cells. The antioxidant defence enzyme activities responsible for scavenging the free radicals and maintaining the redox homeostasis, such as SOD (Superoxidase dismutase), CAT (Catalase), and GSH (Glutathione) are decreased in diabetic retina. The level of this intracellular antioxidant (GSH, SOD, CAT) decreased in retina in diabetes. Finally, due to imbalance between pro-oxidant (Vitamin C and E) and antioxidant (GSH, SOD, CAT) insufficient neutralization of free radicals occurs and causes oxidative stress.

(v) Angiogenic Mechanism in Diabetic Retinopathy

(a). Vascular endothelial growth factor
(b). Protein Kinase C -beta (PKC-β)

(vi). Inflammation in Diabetic Retina

(a) IL-1 β : Progressive Diabetic retinopathy increases the adhesion of the leucocytes to the endothelial cells.
(b) Tumor Necrosis Factor: TNF alpha is the prototype member of the family cytokine it includes Fas Ligand (FasL), CD40 ligand and TNF-alpha related apoptosis inducing ligand (TRAIL) and induce apoptosis, cell differentiation and activation. TNF-α directly involved in the inflammation of endothelial cell and be used as the biomarkers for early detection of diabetic Retinopathy.

(vii) Apoptosis In Diabetic Retina

(a) Bax/Bcl-2

It is observed that Bax was more widely expressed in the conjunctiva of the patient then Bcl2 with and without diabetic retinopathy and further conductive to apoptosis in the presence of hyperglycaemia.

(b) Caspase-3

The most studied cell death type in diabetic retinopathy is apoptosis. Depending on cell types active caspase-8 initiate one or more pathways first executioner of caspase 3. Another type of apoptosis called intrinsic apoptosis in which eventual execution of caspase 3. Intrinsic apoptosis initiated by intracellular stress both extrinsic and extrinsic pathways run near mitochondrion.

(c) Basement Membrane Thickening in Diabetic Retina

The vascular basement membrane thickening is the fundamental modification of small blood vessels in diabetes. Basement membrane is degraded by matrix metalloprotease.

Kumar et al., 2013, found that due to its complicated pathogenesis, the study on the process of the development of DR has been a hotspot. There are already some reports about the establishment of the rat model of streptozotocin (STZ)-induced DR.

Prevention / Treatment of Metabolically Induced Retinal Diseases

The three most common therapies for DR today are retinal photocoagulation, anti-vascular endothelial growth factor (VEGF) therapy, and vitrectomy, however, there are a number of drawbacks and limits to these methods.

Teo et al., 2021, Current treatments for DR include laser surgery and intraocular injections of anti-vascular endothelial growth factor (VEGF) agents, which aim to reduce proliferative diabetic retinopathy and macular edema.
Tong et al., 2022, found that in some patients, these treatments are only temporarily effective, and retinopathy may continue to progress, leading to further vision loss. In cases of severe fundus hemorrhage or vitreo-retinopathy, vitrectomy is commonly employed with certain associated risks. At the same time, the preventive and therapeutic role of complementary alternative medicine for DR has been increasingly recognized.

**Role of Herbal Drugs in the Treatment of Diabetic Retinopathy**

Herbal medicine is currently enjoying a revival in popularity in the west and in many parts of the world. In ethnopharmacology about 1000 plants possess anti-diabetic potential. Herbal drugs are gaining importance is recognized for prophylactic and preventive therapy. Surprisingly, a more recent survey revealed that more than 50 % of all prescription drugs issued by rational physicians are either directly derived from the natural sources or synthesized from the natural products. It seems certain that the continued scientific study of medicinal plants afford a plethora of novel, structurally diverse and bioactive compounds.

Current therapies for diabetic retinopathy (DR) incorporate blood glucose and blood pressure control, vitrectomy, photocoagulation, and intravitreal injections of anti-vascular endothelial growth factors or corticosteroids. The pathophysiology of DR is not fully known, but there is more and more evidence indicating that oxidative stress is an important mechanism in the progression of DR. In this sense, antioxidants have been suggested as a possible therapy to treat DR.

Pandita and Vaidya (2014), illustrated that the phenolic compounds show a wide range of therapeutic potentials such as antioxidant, anti-inflammation, and antidiabetic effects. In addition, it has been demonstrated that polyphenolics such as quercetin and the substances which are rich in polyphenolic compounds can improve diabetic retinopathy.

Arikan et al., 2015, curcumin and β-glucogallin one of the principal compounds from Curcuma longa and Emblica officinalis have shown therapeutic potentials in Diabetic retinopathy. Curcumin and β-glucogallin may increase insulin sensitivity, decrease insulin resistance, and enhance glucose and lipid metabolism in diabetic and DR patients by lowering oxidative stress and inflammatory pathway conditions. Besides, they have been shown potent anti-apoptotic, anti-inflammatory, antioxidant, anticancer, and pro-vascular function.

(i) **Turmeric (Curcuma Longa)**

Curcumin (diferuloylmethane), the main bioactive component of turmeric, has been shown to possess antiangiogenic properties against SDF-1α. Curcumin has potential benefits in the prevention of retinopathy in diabetic patients.

(ii) **Fenugreek (Trigonella foenum-graecum)**

Fenugreek treated retina have a marked decreased in the level of inflammation and angiogenic biomarkers. Amino acid has been extracted and purified from fenugreek seeds, which are known in traditional medicine for their antidiabetic
properties.

(iii) Tulsi (Ocimum Santum)
A combination of Vitamin E and Ocimum santum treatment also reported to reverse the change of Diabetic Retinopathy.

(iv) Quercetin
Diabetic retinopathy being a malnutrition disorder, dietary supplement can be helpful to check its progressive effects. Quercetin treated rat shows a decrease in the level of Caspase-3 in diabetic Retina. The basement Membrane thickness is also less in quercetin treated rat. It is widely reported for its antioxidant and anti-inflammatory properties. It shows that this bioflavonoid possesses retinal neuroprotective effect.

(v) Green Tea (Camellia sinensis)
Green tea (GT) possesses anti-inflammatory, antioxidative and anticarcinogenic properties. The catechins present in GT are commonly known as polyphenols and are flavanols in nature. Tea polyphenols such as epigallocatechin gallate (EGCG) have cryoprotective properties such as inhibition of pro-inflammatory cytokines and inhibition of growth factors by inducing neovascularization. Green tea restores the antioxidant defence mechanism of Retina back to the normal. Green tea has potential to save the diabetic Retina.

(vi) Hesperetin
Hesperetin is a common flavonoid found in the citrus fruit (powerful free radical scavenger) useful in diabetic retinopathy.

(vii) Tinospora cordifolia Willd.
Tinospora cordifolia reduced the expression of PKC hence VEGF is also regulated. Inhibition of TNF-α and IL-1β by Tinospora cordifolia possess protective effect.

(viii) Ginkgo biloba
The various pharmacological activities of G. biloba include antioxidant, neuroprotective and blood flow-improving properties make it a potential candidate for its utilization in the prevention of diabetic retinopathy.

Table 3: Mechanism of action of Herbs in DR. (Behl et al., 2017)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Herbal Drug</th>
<th>Major Constituent</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Curcuma longa</td>
<td>Curcumene, Curcumenone, Curcone, Curdione, Cineole, Curzerenone, eugenol, epiprocurcumenol, Camphene, Camphor, Procurcumenol, Bornel, Procurcumadiol, Curcumin, unkonan A, B, &amp; D, B- sitosterol</td>
<td>anti-oxidant, possess antiangiogenic properties against SDF-1α.</td>
</tr>
<tr>
<td>2.</td>
<td>Trigonella foenumgraecum</td>
<td>4-hydroxyisoleucine</td>
<td>Anti-inflammatory, anti angiogenic</td>
</tr>
<tr>
<td>3.</td>
<td>Ocimum sanctum</td>
<td>Eugenol</td>
<td>antioxidant</td>
</tr>
<tr>
<td>4.</td>
<td>citrus fruits, apples, onions, parsley, sage, tea, and red wine, Olive oil, grapes, dark cherries, and blueberries and blackberries</td>
<td>Quercetin</td>
<td>antioxidant, antiapoptotic and antiinflammatory property</td>
</tr>
<tr>
<td>5.</td>
<td>Camellia sinensis</td>
<td>epigallocatechin</td>
<td>anti-inflammatory, anti-oxidative and anti-carcinogenic</td>
</tr>
<tr>
<td>6.</td>
<td>Citrus fruit</td>
<td>Hesperetin</td>
<td>anti-apoptotic, antioxidant and anti-inflammatory</td>
</tr>
<tr>
<td>7.</td>
<td>Tinospora Cardifolia</td>
<td>(-) Epicatechin, Tinosporin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Panax notoginsen</td>
<td>ginsenoside, ginsenoside Rd, ginsenoside Rg1, ginsenoside Rb1 and Notoginsenoside R1</td>
<td>antioxidant</td>
</tr>
<tr>
<td>9.</td>
<td>Litsea japonica</td>
<td>lactones, alkaloids, essential oils, fatty acids, and terpenoids</td>
<td>Antioxidant and anti-apoptotic</td>
</tr>
<tr>
<td>10.</td>
<td>Ginkgo biloba</td>
<td>Biflavones, terpene trilactones (ginkgolides A, B, C, J, P and Q, and bilobalides), quercetin, catechin and Pro-anthocyanidins</td>
<td>Down regulate the expression of PAF Reduce the expressions of HIF-1α and VEGF</td>
</tr>
</tbody>
</table>

References