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PHYTOCHEMICALS AND COMPLICATIONS IN TYPE 2 DIABETES-AN UPDATE

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ABSTRACT: Type 2 diabetes is a serious health problem globally. In type 2 diabetes insulin resistance in various tissues such as liver, muscle and β -cell is the major pathophysiological defects. People with long term uncontrolled hyperglycemia are at risk of developing a number of serious and life-threatening complications which mainly affect the heart and blood vessels, eyes, kidneys, and nerves. Current drug development strategy has focused towards the control of hyperglycemia but the treatment of severe complications has been neglected. Many herbs including *Momordica charantia*, *Coccinia indica*, *Ficus carica*, *Gymnema sylvestre*, *Ocimum santum* and many more have traditionally been used for the treatment of diabetes and associated complications. Natural products have been reported to have their efficacy in diabetes and its complications by protecting pancreatic β -cells, increasing insulin sensitivity, reducing oxidative stress and by targeting various proteins. Thus, now a day plant based natural product (phytoconstituents) have been the basis of drug development program for the treatment of various diseases. The present review summarizes the latest updates on phytochemicals from different class of secondary metabolites with potential effect in type 2 diabetic complications.

INTRODUCTION: Type 2 diabetes is a serious global health problem accounts for 80 % to 95 % of all reported diabetes cases. As per World Health Organization 382 million people worldwide are estimated to have diabetes and it will reach up to 592 million by 2035. Epigenetic, genetic and environmental factors play a major role in the development of T2D ¹. T2D diabetes is generally associated with specific complications which include microvascular and macrovascular complications ².

Microvascular complications include nephropathy (renal damage), neuropathy (nervous system damage) and retinopathy (eye damage). Macrovascular complications include peripheral artery disease, cardiovascular disease, and cerebrovascular disease. The prevalence of microvascular complications is higher than the macrovascular complications in type 2 diabetic patients ³. Diabetic nephropathy is the foremost cause of end-stage renal disease in type 2 diabetic patient. It is characterized by proteinuria greater than 500 mg/ 24 hrs followed by further developments of overt albuminuria and ultimately causes renal failure along with hypertension and progressive renal function loss ⁴.

Additional features of diabetic nephropathy include thickening of glomerular basement membranes, glomerular hyper filtration, expansion of mesangial matrix and increase in urinary albumin excretion

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which causes glomerular and tubular sclerosis and renal failure⁵. In type 2 diabetes patient retinopathy starts to develop within 7 years before the diagnosis of diabetes in patients. Diabetic retinopathy can damage peripheral retina, macula or both. This leads to visual disability and blindness. DR categorized as nonproliferative and preproliferative to severely proliferative which is characterized by abnormal growth of new vessels. Vitreous hemorrhage or retinal detachment causes partial or total vision loss while retinal vessel leakage and macular edema causes central vision loss. Duration of diabetes is the most significant predictor of visual impairment among people with type 2 diabetes⁶.

The major risk factor for diabetes neuropathy is hyperglycemia. Nearly 50% of individuals with diabetes have some form of peripheral neuropathy (PN), either polydiabetic or monodiabetic neuropathy. Some individuals with diabetes are also associated with autonomic neuropathy, with cardiovascular autonomic dysfunction. Peripheral neuropathy characterized by axonal thickening, basement membrane thickening, pericyte loss, loss of microfilaments and decreased capillary blood flow to C fibers, which reduced nerve perfusion and endoneurial hypoxia. Hyperglycemia causes impairment of neuronal microvasculature which further leads to demyelination associated with diabetic PN. Cardiac autonomic neuropathy causes tachycardia, resting HR variability, slow HR recovery after exercise and myocardial infarction. It is also associated with the development of cardiomyopathy⁷.

In type 2 diabetes, cardiovascular disease is the major cause of morbidity and mortality. Approximately 80 % of the diabetic patient dies because of cardiovascular events such as coronary heart diseases as well as peripheral or other macrovascular disease. The major responsible factors for the development of cardiovascular events includes persistent hyperglycemia which ultimately promotes lipogenesis and increases total and low-density lipoprotein(LDL), cholesterol and triglyceride level along with altered platelet function and increased glycoprotein metabolism⁸. Insulin mediated production of endothelium derived nitric oxide is also reduced in T2D leads to

athreogenesis. Insulin resistance also reduces the expression of VEGF in myocardium which leads to vascular smooth muscle cell proliferation and thrombosis. Sudden death from stroke is an independent risk factor of diabetes. Carotid artery atherosclerosis in diabetic patient significantly affects cerebrovascular circulation. Fatal and non-fatal stroke is also associated with hyperglycemia and hyperinsulinemia. High blood level of inflammatory markers is also responsible factor for stroke in diabetic patients. Peripheral artery disease is another major complication in diabetes. Occlusion of the arteries in lower extremity is the common indication of peripheral artery disease. This is followed by intermittent claudication and pain specifically after exercise. It further causes functional impairments and disability. Long term uncontrolled hyperglycemia also leads to foot ulcers and amputation of lower extremities⁹.

Long term hyperglycemia and insulin resistance is the common risk factor for the development diabetic complications. Hyperglycemia activate aldose reductase pathway, hexosamine pathway, protein kinase C and mitogen activated protein kinases. It also increases the expression of various growth factors such as tumor necrosis factor-alpha, platelet-derived growth factor, insulin like growth factor and vascular endothelial growth factor^{8, 10}. Uncontrolled hyperglycemia also produces reactive oxygen species (ROS) and it is a major risk factor for both microvascular and macrovascular complications by further activation of cascade of transcription events followed by changes in cytokines and nitric oxide levels. It also activates transduction of intracellular signal which leads to oxidation of lipid, proteins and nucleic acids¹¹.

Plants are the rich source of medicines. Phytoconstituents obtained from the plants are used for centuries to treat various ailments. They have physiological role in the living flora hence they are believed to have compatibility with human body and are considered to be safe¹². There are various classes of phytoconstituents present in the plant. Alkaloid increases the secretion of insulin in the pancreas by inhibiting alpha-glycosidase¹³. Flavonoids are potent antioxidant which also inhibits formation of advanced glycation end product and also act as aldose reductase inhibitor. Saponin regulates glucose and lipid metabolism

and control hyperlipidemia and hyperglycemia¹⁴. Many phytoconstituents are studied for its antidiabetic and diabetic complications. There are many reviews related to diabetes, its complications and herbal medicines including phytoconstituents. The current review provides an update on phytochemicals from different class of secondary metabolites with potential effect in type 2 diabetic complications.

2. Role of phytoconstituents:

2.1 Alkaloids:

Oxymatrine:

Oxymatrine is a quinolizidine alkaloid extracted from the root of *Sophora flavescens* (Family Fabaceae), a Chinese herb. Guo et al studied oxymatrine in type II diabetic high-fat diet streptozotocin (HFD-STZ), nephropathy model at an oral dose of 150 mg/kg/day for 11 weeks. They found that it significantly decreases blood glucose, urinary protein and albumin excretion, serum creatinine, and blood urea nitrogen in diabetic rats, and ameliorates diabetes-induced glomerular and tubular pathological changes. It significantly prevented oxidative stress and reduced the contents of renal advanced glycation end products, transforming growth factor- β 1, connective tissue

growth factor, and inflammatory cytokines in diabetic rats¹⁵. **Fig.1.**

Boldine:

It is an aporphine benzyloquinoline class of alkaloid isolated from the leaves and bark of the *Peumus boldus* Moliba (Chilean boldo tree, family Monimiaceae). It is a potent natural antioxidant. Lau and coworkers found that oral treatment of boldine at the dose of 20 mg/kg for seven days in db/db mice or incubation of mouse aortic endothelial cells with 1 μ mole/l of boldine for 12 hr enhanced endothelium-dependent relaxation in aortas. It also reduced overproduction of reactive oxygen species by inhibiting Ang II-stimulated BMP4 expression¹⁶.

Neferine:

It is an alkaloid of the class bisbenzyl isoquinoline obtained from the *Nelumbo nucifera* Gaert (Nelumbonaceae). Li and coworker observed reduced expression of CCL5 and CCR5 mRNA in the superior cervical ganglion of type 2 diabetic rats after treatment with neferine 4 mg/kg for 4 weeks. It also decreased body weight, fasting blood glucose, blood pressure, total cholesterol and triglyceride and increased high density lipoprotein¹⁷.

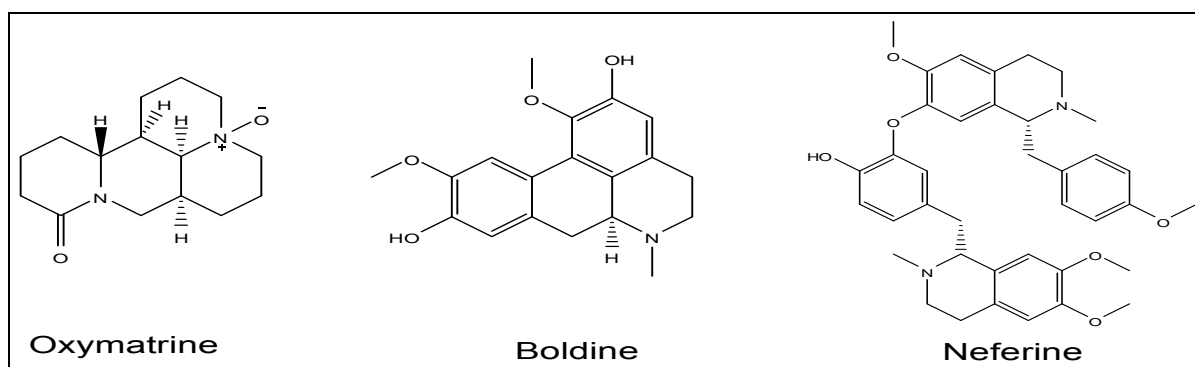


FIG.1: ALKALOIDS FROM DIFFERENT CLASS STUDIED FOR COMPLICATIONS IN TYPE 2 DIABETES

2.2 Flavonoids:

Silymarin:

Silymarin is a unique flavonoid complex containing silybin, silydianin, and silychrisin derived from the milk thistle plant. Sheela and coworkers evaluated the effect of Silymarin in streptozotocin and nicotinamide induced Non-insulin-dependent diabetes mellitus rats. After 60 days treatment of rats with 120 mg/kg of silymarin, there was significant reduction in levels of blood glucose,

glycosylated hemoglobin, urine volume, serum creatinine, serum uric acid, and urine albumin, compared to the diabetic control group. These findings supported nephroprotective effects of Silymarin in type 2 diabetes mellitus¹⁸. **Fig. 2**

Rutin:

It is a flavonoid glycoside generally present in certain fruits and vegetables. The protective effect of rutin on the glomerulosclerosis

of diabetic nephropathy (DN) in rat mesangial cells was investigated by Tang et al. they found that rutin significantly decreased the cell percentages of the G₀/G₁ phase and inhibited the expression of Smad 2/3, laminin and type IV collagen, and TGF- β ₁ mRNA level. The antioxidant capacity, the cell percentages of S phase and Smad 7 expression were also significantly increased by rutin¹⁹.

Chrysin:

It is a naturally occurring flavone found in the passion flowers *Passiflora caerulea* and *Passiflora incarnata*, and in *Oroxylum indicum*. Ahad et al., investigated the nephroprotective effects of chrysin (5, 7-dihydroxyflavone) in a high fat diet/streptozotocin (HFD/STZ)-induced type 2 diabetic rat model and revealed that chrysin prevents the development of DN through anti-inflammatory effects in the kidney by specifically targeting the TNF- α pathway. The treatment with chrysin for 16 weeks post induction of diabetes significantly abrogated renal dysfunction and oxidative stress. It also improved renal pathology and suppressed transforming growth factor-beta (TGF- β), fibronectin and collagen-IV protein expressions in renal tissues and significantly reduced the serum levels of pro-inflammatory cytokines, interleukin-1beta (IL-1 β) and IL-6²⁰.

Quercetin:

Quercetin is a flavonol found in many fruits, vegetables, leaves and grains. Chen and coworker studied the nephroprotective effect of Quercetin in high fat diet/streptozotocin (HFD/STZ)-induced type 2 diabetic rat model. The expressions of ubiquitin and NF- κ B p65 determined by immunohistochemical method in renal tissues of quercetin treated group increased significantly²¹. Quercetin's protective effects on the glomerulosclerosis of diabetic nephropathy (DN) in rat mesangial cells was also investigated. It significantly decreased the cell percentages of G₀/G₁ phase, Smad 2/3 expression, laminin and type IV collagen, and TGF- β (1) mRNA level. The antioxidant capacity, the cell percentages of S phase and Smad 7 expression was significantly increased by quercetin²². Li XH and coworkers evaluated the effectiveness of Pentamethyl quercetin (PMQ) for ameliorating diabetes-related cognitive dysfunction *in vivo* and *in vitro*.

Treatment with PMQ in GK rats significantly ameliorated cognitive deficits and neuronal damage and increased dendritic spine density, by improving insulin resistance and metabolic disorders. It inhibited high glucose-induced cellular toxicity and significantly activated the Akt/cAMP response element-binding protein pathway and increased the expression of memory-related proteins in the downstream part of the Akt/cAMP response element-binding protein pathway, such as synaptophysin and glutamate receptor 1²³.

Naringenin:

Naringenin is a flavanone predominantly found in grapefruit, having antioxidant, anti-inflammatory, carbohydrate metabolism promoter, and immune system modulator properties. Tsai and coworkers examined renal protective effects of naringenin at 1, and 2% of the diet in diabetic mice and they observed that it attenuates diabetic nephropathy via its anti-inflammatory and antifibrotic activities. It significantly reduced plasma glucose level and blood urea nitrogen and increased insulin level as well as creatinine clearance. It also reduced expression of interleukin (IL)-1 β , IL-6, type IV collagen, fibronectin, transforming growth factor- β 1, monocyte chemoattractant protein-1 and reduced protein kinase C activity. Furthermore it suppressed nuclear factor κ B (NF- κ B) p65 activity, mRNA expression, and protein production in kidney²⁴.

Rahigude and co-workers investigated the influence of naringenin at a dose of 50mg/kg against type-2 diabetes-induced memory dysfunction in rats. The memory deficit was assessed by using a novel object recognition paradigm. Naringenin was found to decrease oxidative stress by depleting elevated lipid peroxide and nitric oxide and elevating reduced glutathione levels and showed significant protection and improvement in cognitive behavior against diabetes-induced memory dysfunction and biochemical changes. Cholinergic function was improved by naringenin through the inhibition of elevated ChE activity²⁵.

Baicalein:

Baicalein is a flavonoid present in the stem bark of *Oroxylum indicum* and roots of *Scutellaria*

baicalensis. Ahad et al., investigated the nephroprotective effects of baicalein (BAC), at a dose of 10 mg/kg bw/day and 20 mg/kg bw/day for 16 weeks in HFD-STZ induced type 2 diabetic Wistar rats. Baicalein was found to maintain renal function in diabetic nephropathy by anti-hyperglycemic, antioxidant and anti-inflammatory effects. Baicalein treatment significantly lowered food intake, body weight and fasting blood glucose levels, HbA1c and homeostasis model assessment index (HOMA-IR) in diabetic rats. It was also found to restore normal renal function and mitigate renal oxidative stress and suppress the activation of NF- κ B, decrease expression of iNOS and TGF- β 1, and ameliorate the structural changes in renal tissues, normalize the levels of serum pro-inflammatory cytokines and liver function enzymes²⁶.

Icariin

It is a flavonoid glycoside present in various species of epimedium. Li and coworkers investigated the effect of icariin on excess mesangial type IV collagen and fibronectin accumulation induced by high glucose. It was found to diminish type IV collagen and fibronectin accumulation, in glomerular mesangial cells by inhibiting transforming growth factor- β production and signalling through G protein-coupled oestrogen receptor. It was also found to inhibit TGF- β 1 downstream pathways and TGF- β canonical Smad signalling and extracellular signal-regulated kinase (ERK)1/2 signalling by decreasing Smad2/3 and ERK1/2 phosphorylation in a dose-dependent manner²⁷.

Isoangustone A:

Isoangustone A is anisoflavone present in licorice. Li and coworkers investigated the ability of Isoangustone A to inhibit renal fibrosis and inflammation by high glucose (HG) in human mesangial cells at a dose of 1-20 μ mol/L for three days. It suppressed membrane type matrix metalloproteinase (MMP)-1 expression, diminished HG-elevated tissue inhibitor of MMP-2 expression and TGF- β 1-SMAD-responsive signaling, intracellular cell adhesion molecule-1 (ICAM-1) level and monocyte chemoattractant protein-1 (MCP-1) and mRNA expression. It also reduced mesangial sclerosis associated with inflammation

in response to HG by hampering TGF- β and NF- κ B signaling²⁸.

Isoliquiritigenin:

It is a chalcone type flavonoid obtained from *Glycyrrhiza glabra*. Li and coworker studied isoliquiritigenin for its inhibition ability in high glucose (HG)-induced mesangial fibrosis by retarding formation of type IV collagen as well as CTGF in human mesangial cells (HRMC). They found that it reversed the marked increases in collagen secretion and CTGF expression caused by HG. It also boosted HG-plummeted type matrix metalloproteinase-1 (MT-1 MMP) expression and dampened HG-elevated tissue inhibitor of MMP-2 (TIMP-2) expression, facilitating the degradation of mesangial matrix and diminished mesangial matrix accumulation in response to ambient HG through retarding TGF-beta1-SMAD signaling transduction²⁹.

Diosmin:

It is a flavonoid obtained from hesperidin after dehydrogenation. Jain and coworkers evaluated the nephroprotective effect of Diosmin at a dose of 50 and 100 mg/kg, p.o. for 4 weeks in type II diabetic high-fat diet/ streptozotocin (HFD-STZ), nephropathy model. Treatment with diosmin significantly restored the reduced body weight, elevated blood sugar and lipid profiles and caused improvement in thermal hyperalgesia, cold allodynia and walking function in diabetic rats treated with diosmin. Four weeks of diosmin treatment restored elevated levels of malondialdehyde, nitric oxide and decreased glutathione levels and superoxide dismutase activity³⁰.

Genistein:

Genistein is an isoflavone present in soya and red clover. Babu and coworkers found that pretreatment of human aortic monocyte endothelium cells with genistein (0.1 μ mol/L) significantly inhibits high glucose induced monocyte adhesion to human aortic EC and reduced the production of monocyte chemotactic protein-1 (MCP-1) and IL-8. It also improved the intracellular cAMP production and PKA activity in HAEC. The researchers also measured concentration of MCP-1/IE and KC and IL-10 in

six-week-old diabetic db/db mice after treatment with genistein 1g/kg for 8 weeks. The result of the study showed significant suppression of the elevated serum concentrations of MCP-1/JE and KC along with increased concentration of IL-10³¹.

Anthocyanin (Cyanidin-3-O- β -glucoside):

It is an Anthocyanins present in various fruits, vegetables, red wines and grains. cyanidin 3-glucoside (C3G), is reported to possess potent anti-inflammatory properties. Liu and coworkers investigated the protective effect of cyanidin-3-O- β -glucoside for adiponectin on diabetes-related endothelial dysfunction. cyanidin-3-O- β -glucoside treatment restores endothelium-dependent relaxation of the aorta in db/db mice. It also induces adiponectin expression and secretion in

cultured 3T3 adipocytes through transcription factor fork head box O1 (Foxo1). It significantly improved flow-mediated dilation (FMD) and increased serum adiponectin concentrations in patients with type 2 diabetes³². In another study of Male C57BL/6J obese mice and genetically diabetic db/db mice received dietary C3G supplementation (0.2%) for 5 weeks. C3G was found to lower fasting glucose levels and improved the insulin sensitivity. White adipose tissue messenger RNA levels and serum concentrations of inflammatory cytokines (tumor necrosis factor- α , interleukin-6, and monocyte chemoattractant protein-1) were also reduced by C3G, as did macrophage infiltration in adipose tissue. Hepatic triglyceride content and steatosis were alleviated by C3G³³.

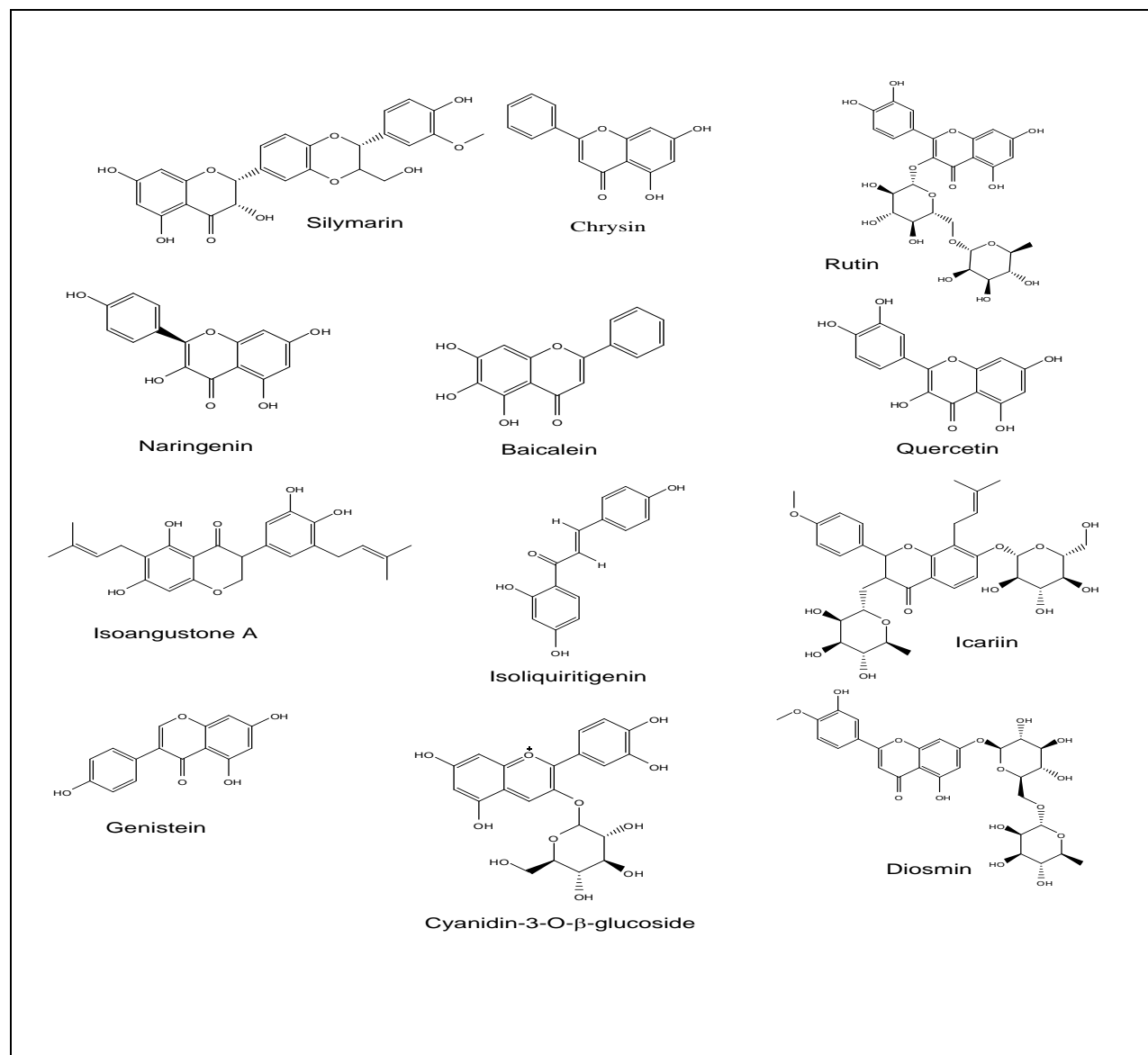


FIG.2: FLAVONOIDS FROM DIFFERENT CLASS STUDIED FOR COMPLICATIONS IN TYPE 2 DIABETES

2.3 Phenylpropanoid:

Oleuropein:

Oleuropein is one of the most important phenolic compounds of olive leaves and is believed to mediate most of the beneficial pharmacological properties of olive oil or leaves. Nekooeian and coworkers found that oleuropein reduced blood glucose, serum malondialdehyde, blood pressure, infarct size, coronary effluent creatine kinase-MB and coronary resistance in type 2 diabetic rats. It also reduced left ventricular developed pressure, erythrocyte superoxide dismutase, rate of rise and rate of decrease of ventricular pressure³⁴. **Fig.3**

2.4 Iridoid glycoside:

Catalpol:

It is an iridoid glycoside first isolated from the genus catalpa. Liu and coworkers found that treatment with catalpol significantly reduced endothelial damage of thoracic aorta, also decreased ROS level of thoracic aorta and serum level of 8-iso-PGF2 α in type 2 diabetic rats. It increased the level of serum NO and SOD and it reduced expression of Nox4, p22phox mRNA and protein in thoracic aorta³⁵.

Loganin:

Yamabe and coworkers studied the effect and mechanism of loganin, a major iridoid glycoside of *Corni Fructus*, on the type 2 diabetic db/db mice at a dose of 20 or 100 mg/kg body weight daily for 8 weeks. Loganin treatment led to amelioration of hyperglycemia and dyslipidemia in both the serum and hepatic tissue; reduction of triglyceride in the kidney and reduction of the enhanced oxidative stress and augmentation of the oxidized to reduced glutathione ratio (liver and kidney). Furthermore, loganin inhibited advanced glycation end product formation and the expression of its receptor, and nuclear factor-kappa B-induced inflammation in the hepatic tissue of db/db mice³⁶.

Swertiamarin:

It is a seco-iridoid glycoside present in *Enicostemma littorale* Blume (Gentianaceae). Vaidya and coworkers found that administration of 50 mg/kg dose of swertiamarin for 6 weeks in type 2 diabetic rats reduced the level of serum triglycerides, cholesterol and low-density lipoprotein levels. It significantly reduced fasting glucose level and increased insulin sensitivity index after treatment with swertiamarin³⁷.

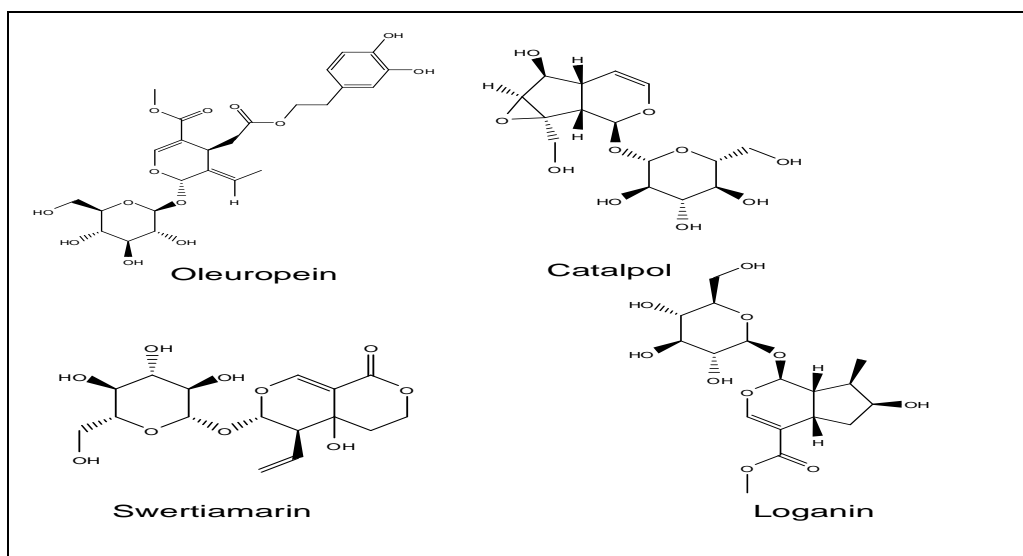


FIG. 3: PHENYLPROPANOID AND IRIDOID GLYCOSIDE FROM DIFFERENT CLASS STUDIED FOR COMPLICATIONS IN TYPE 2 DIABETES

2.5 Saponins:

Astragaloside IV: It is a 3-O- β -D-xylopyranosyl-6-O- β -D-glucopyranosyl cycloastragenol present in Chinese medical herb *Astragalus membranaceus* (Fabaceae). Jiang and coworkers found that Astragaloside -IV inhibited TNF alpha-induced

accelerated lipolysis in a dose-dependent manner, which was compatible with suppressed phosphorylation of ERK1/2 and reversed the downregulation of perilipin. Furthermore, it also ameliorated TNF alpha induced down regulation of key enzymes in lipogenesis, including LPL, FAS

and GPAT and improved TNF α -induced insulin resistance in 3T3-L1 adipocytes³⁸. **Fig. 4**

2.6 Triterpenoid:

Ursolic acid:

Ursolic acid (UA) is a pentacyclic triterpenoid compound naturally occurring in fruits, leaves and flowers of medicinal herbs. Lee J investigated the dose-response efficacy of UA (0.01 and 0.05%) on glucose metabolism, the polyol pathway and dyslipidemia in streptozotocin/ nicotinamide-induced diabetic mice. Supplement with ursolic acid reduced fasting blood glucose and plasma triglyceride levels and significantly lowered plasma free fatty acid, LDL-cholesterol levels, total cholesterol and VLDL-cholesterol levels. It effectively decreased hepatic glucose-6-phosphatase activity and increased glucokinase activity, the glucokinase/glucose-6-phosphatase ratio, GLUT2 mRNA levels and glycogen content and attenuated hyperglycemia-induced renal hypertrophy and histological changes³⁹.

2.7 Stilbenoid (polyphenol):

Resveratrol:

It is a polyphenol produced in various plants in response to environmental stress. Beaudoin and coworkers found that treatment of type 2 ZDF rats with 200 mg/kg of resveratrol reduced the risk of development of diabetic cardiomyopathy by reducing fibrosis, palmitoyl-CoA respiratory sensitivity, mitochondrial reactive oxygen species emission rates and reactive lipid accumulation⁴⁰.

(-)-Epigallocatechin – 3 - gallate (catechin-polyphenol):

It is the key component of the polyphenolic fraction of green tea. Liu and groups found that (-)-epigallocatechin-3-gallate attenuated myocardial mitochondrial dysfunction by regulating FOXO factors and elevated autophagy in the heart of diabetic Goto-Kakizaki (GK) rats after administration of 100 mg/kg dose for 12 weeks⁴¹.

Oligonol:

Oligonol is a patented, low-molecular-weight polyphenol derived from lychee fruit (85%) and green tea (15%). Park et al., studied the effect of Oligonol in db/db mice with type 2 diabetes at an oral dose of 10 or 20 mg/(kg body weight for 8

wk. Oligonol was found to decrease the elevated renal glucose concentrations and reactive oxygen species, serum urea nitrogen and creatinine concentrations in db/db mice. It also improved the expressions of antiapoptotic B-cell lymphoma protein 2 (Bcl-2) and survivin and proapoptotic [Bcl-2-associated X protein, cytochrome c, and caspase-3] proteins in the kidneys of db/db mice⁴².

In another study carried out by Noh and group found that treatment of Oligonol(10 or 20 mg/kg) for 8 weeks to db/db mice reduced the level of reactive oxygen species (ROS), lipid peroxidation, and the TAG and total cholesterol concentrations in both the serum and liver and attenuated oxidative stress through the inhibition of advanced glycation endproduct formation and its receptor expression⁴³.

Salvianolic acid A:

Salvianolic acid A (SalA) has been reported to be a strong polyphenolic anti-oxidant and free radical scavenger. Qiang and coworkers evaluated the effect of SalA at a dose of 0.3 mg/kg/day for four months on the pathological progression of hepatic fibrosis in high-fat diet (HFD)-fed and streptozotocin (STZ)-induced diabetic rats. After administration, SalA reversed the hyperlipidemia and reduced hepatic triglyceride (TG) with the reduction of type I and III collagens. SalA also improved hepatic mitochondrial respiratory function in diabetic rats. These findings demonstrated that SalA could prevent the pathological progression of hepatic fibrosis in HFD-fed and STZ-induced diabetic rats. The underlying mechanisms proposed are reduction in oxidative stress, suppression of α -SMA and TGF- β 1 expression, and anti-apoptotic and mitochondria-protective effects⁴⁴.

2.8 Miscellaneous:

Cannabidiol:

Cannabidiol (CBD) is a naturally occurring molecule found in the plant *Cannabis sativa* (Cannabaceae). Wheal and group found that CBD at the concentration of 10 μ M enhanced the maximum vasorelaxation to acetylcholine (ACh) in femoral arteries and this enhancement persisted after cannabinoid receptor (CB) type 1, endothelial CB, or peroxisome proliferator-activated receptor- γ antagonism but it was inhibited by CB2 receptor

antagonism. CBD also enhanced the activity of both purified COX-1 and COX-2 which is responsible for vasodilation⁴⁵. Rajesh and coworkers also found that cannabidiol at the dose of 20 mg/kg reduced myocardial dysfunction, cardiac fibrosis, oxidative/nitrative stress,

inflammation, cell death, and interrelated signaling pathways in type 2 diabetic C57/BL6J mice. Moreover CBD (4 μ M) also attenuated the high glucose-induced increased reactive oxygen species generation, nuclear factor- κ B activation, and cell death in primary human cardiomyocytes⁴⁶.

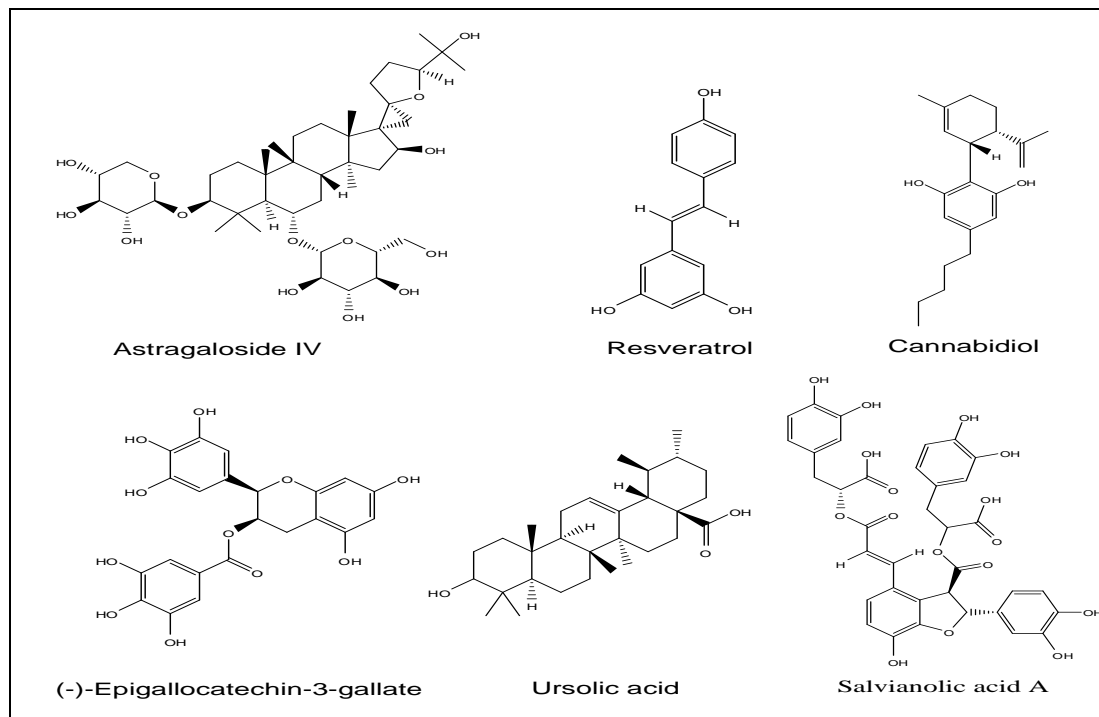


FIG.4: SAPONINS, TRITERPENOIDS, STILBENOIDS AND MISCELLANEOUS CLASS OF PHYTOCONSTITUENTS STUDIED FOR COMPLICATIONS IN TYPE 2 DIABETES

CONCLUSION: In the review, current findings on use of phytoconstituents for the treatment of complications in type 2 diabetes have been discussed. In total 26 phytoconstituents from different class of secondary metabolites have been discussed which includes *in vitro*, cell culture and *in vivo* studies specifically in type 2 diabetic models. Naringenin, and quercetin were reported to be effective in nephropathy as well as diabetes-induced memory dysfunction. Majority of the phytoconstituents were found to be effect in reducing oxidative stress which is a major risk factor for microvascular as well as macrovascular complications. Thus it proves the potential of natural products in treatment of complications in type 2 diabetes mellitus. Several of the reported phytoconstituents are studied for their efficacy in treatment of type 2 diabetes mellitus but not for their complications. These findings of phytochemicals can lead to several potential drug candidates in the future for the treatment of complications in type 2 diabetes mellitus.

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