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Role of Flavonoids and Saponins in the Treatment of Diabetes Mellitus

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ABSTRACT:

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycemia due to insufficient or inefficient insulin secretory response. This chronic disease is a global problem and there is need for greater emphasis on therapeutic strategies in the health system. Current synthetic agents and insulin used effectively for the treatment of diabetes are expensive and have prominent adverse effects. Complementary and alternative approaches to diabetes management such as isolation of phytochemicals with anti-hyperglycemic activities from medicinal plant are therefore imperative. Phytochemicals such as flavonoids and saponins have recently attracted attention as source materials for the development of new anti-diabetic drugs or alternative therapy for the management of diabetes and its related complications. This paper emphasis on the investigations that explore the role of these compounds (flavonoids & saponins) for anti-diabetic remedy.

KEY WORDS: Hyperglycemia, flavonoids, antioxidant activity, saponins.

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INTRODUCTION:

Diabetes mellitus is the world's largest endocrine disease characterized by chronic hyperglycemia associated with abnormalities in carbohydrate, fat and protein metabolism caused by complete or relative insufficiency of insulin secretion and/or insulin action, and usually accompanied by a variety of micro vascular, macro vascular, neurologic and infectious complications. The International Diabetes Federation (IDF) released data showing that a 382 million people worldwide suffered from diabetes in 2013, if this trend will be continued than 592 people may have diabetes by the year of 2035. [1]

Treatment of diabetes mellitus involves diet control, exercise and the use of insulin and oral hypoglycemic drugs. However, they usually have decreased efficacy over time, ineffectiveness against some long term diabetic complications and low cost effectiveness. [2] Because of perceived effectiveness, minimal side effects in clinical experience and relatively low cost, herbal drugs are recognized as a wonderful source for medicines. [3]

Enthnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity. [4, 2] Literature has shown specific chemical constituents of these plants, such as flavonoids and saponins to be the active hypoglycemic and hypolipidemic principle in many medicinal plants with blood glucose and lipid lowering attributes. [5]

Many of the research revealed that flavonoids, which is the main component extracted from some plant have the potential to attenuate the glucose metabolism disorder & act as powerful anti-diabetic as well as antioxidant therapy (example include Musa paradisiacal, Selaginella tamariscina, Tridax procubens etc.) Likewise, saponins isolated from various plants have been used in the treatment of diabetes. (Example include Dioscorea rotundata, Panax notoginseng, Terminalia arjuna etc.) [6, 7, 10, 13, 22, 30, 33]

Flavonoids are polyphenolic compounds that are abundantly found in many herbs. Flavonoids are found to act on various molecular targets and regulate different signalling pathways in pancreatic β-cells, hepatocytes, adipocytes and skeletal myofibres. The role of flavonoids is quite important in diabetes due to their ability to terminate free radicals and reduce the oxidative stress. Flavonoids present in the plants have also shown to regenerate the damaged β-cells of pancreas in some studies. [6]

Saponins present in the plant have a protective effect on pancreatic islet cells and increase insulin secretion from the remaining pancreatic β-cells. Ability of saponin to reduce elevated plasma blood glucose makes saponin an excellent candidate in the treatment of diabetes mellitus. [14]

Therefore, the aim of the present review is to collect some available data on flavonoids and saponins isolated from medicinal plant as the important phytochemical constituents in plants with antidiabetic effect.

2. FLAVONOIDS AND HYPERGLYCEMIA

Flavonoids are polyphenolic compounds that are abundantly found in many herbs. Flavonoids are classified as flavan-3-ols, flavanones, flavonols, anthocyanidins, flavones and isoflavones. Epidemiological, in vitro and animal studies support the beneficial effects of dietary flavonoids on glucose and lipid homeostasis. Flavonoids are found to act on various molecular targets and regulate different signaling pathways in pancreatic β- cells, hepatocytes, adipocytes and skeletal myofibres. Flavonoids may exert beneficial effects in diabetes by

i. Enhancing insulin secretion and reducing apoptosis and promoting proliferation pancreatic β-cells

ii. Improving hyperglycemia through regulation of glucose metabolism in hepatocytes iii. Reducing insulin resistance, inflammation and oxidative stress in muscle and fat

iv. Increasing glucose uptake in skeletal muscle and white adipose tissue.

2.1 Hypoglycemic potential of flavonoids

1) Musa paradisiacal flavanoid rich fraction

Supplementation of Musa paradisiacal at the dose of 200 mg/kg body weight significantly reduced the oxidative stress and hyperglycemia in diabetic rats. Supplementation of this plant was shown to be effective in diabetic complications. This may be mediated by the cumulative action of gallic acid, quercetin and epicatechin in the plant. [7]

2) Murraya paniculata- total flavonoids in diabetic nephropathy

This study showed for the first time, total flavonoids extracted from Murraya paniculata leaves can effectively control or prevent the development of kidney damage in diabetic rats. And the effects of TFMP on Diabetic nephropathy may be via its regulation of glucose, lipid metabolism and oxidative stress. [8]

3) Polygonatum odoraum flavonoids (TFP)

This study demonstrated that 9 day treatment with TFP significantly reduced fasting blood glucose levels in streptozotocin induced type 1 diabetic mice. The result also showed that the blood glucose levels in treated groups were steadily lowered during the whole experiment. In another experiment, 30 day administration with TFP can prevent and reduce remarkably hyperglycemia in type 2 diabetic rats induced by alloxan. [9]

4) Selaginella tamariscina flavonoids

Total flavonoids of Selaginella tamariscina (TFST) had the potential to attenuate the glucose metabolism disorder and nearly normalized the lipid metabolism. These changes may be related to the elevation of the levels of PPAR- γ in adipose tissue and IRS-1 in skeletal muscle and hepatic tissue, increasing of insulin sensitivity and improvement of insulin signal transduction in target

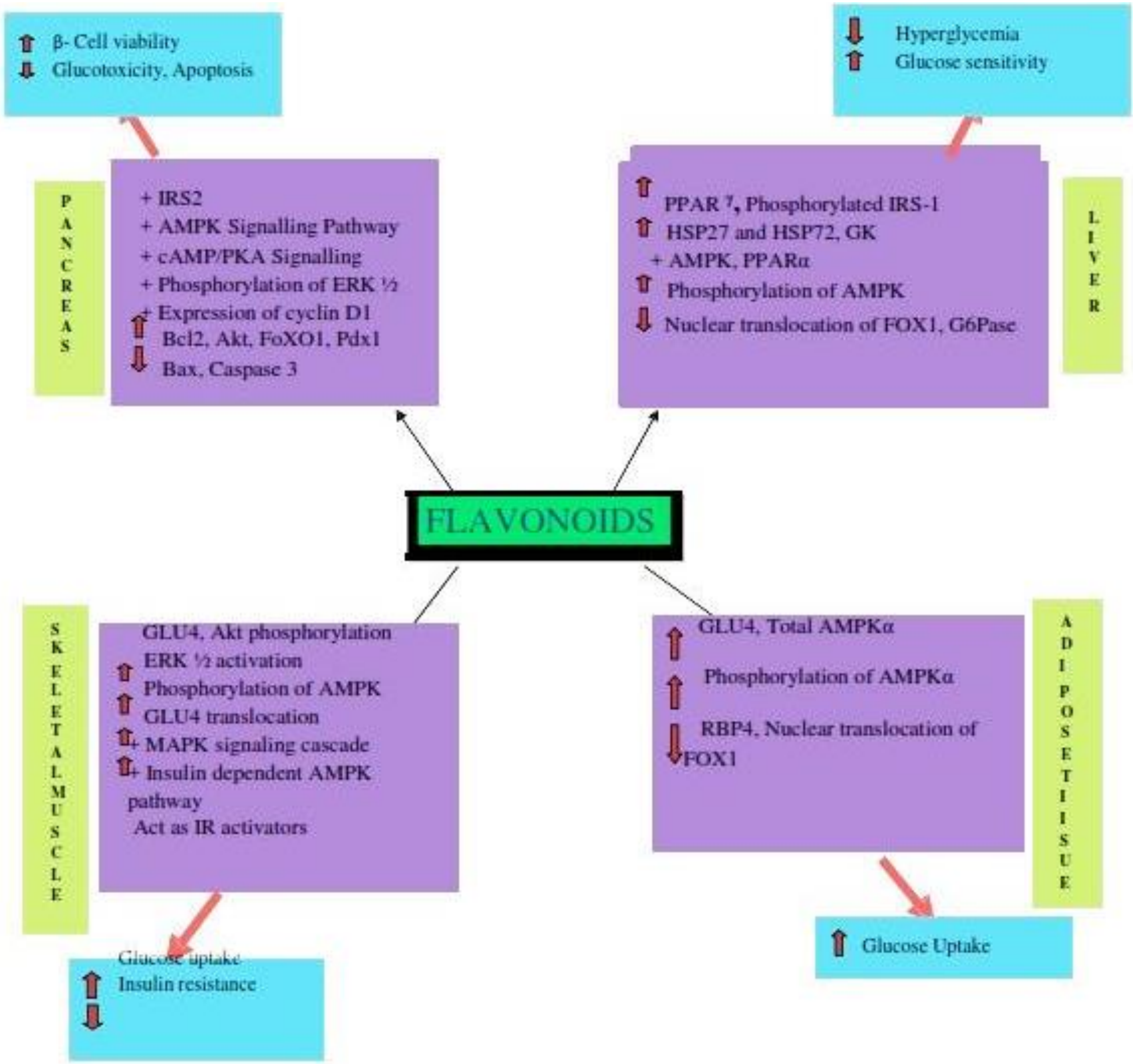

Figure 1 – Role of flavonoids in the treatment of Hyperglycemia by targeting various cellular pathways in pancreas, liver, skeletal muscle and white adipose tissues [6]

tissues, as well as regulation of the insulin and glucagon secretion by TFST treatment. [10]

5) Sedum dendroideum (SD) –kaempferitrin flavonoid

This study demonstrated that SD has hypoglycemic potential in both DM1 and DM2. Its hypoglycemic activity is probably due to the glycosylated flavonol kaempferitrin. This flavonoid is able to modulate 6-phosphofructo-1-kinase (PFK) activity in the major tissues responsible for the control of glycemia: skeletal muscle, liver and adipose tissue from normal and STZ induced diabetic mice. This result showed that the flavonoid is probably able to stimulate cellular glucose utilization in these tissues. [11]

6) Tridax procubens

Ethanolic extract of the whole plant of T. procubens (250 and 500 mg/kg) showed significant anti diabetic activity after two weeks of administration. The anti-diabetic effect of T. procubens might be presence of flavonoids. Flavonoids present in the plant regenerate the damaged beta cells of pancreas, and the polyphenolic compounds and saponin present in the plants inhibit glucose transport by inhibiting sodium glucose co-transporter-1 in intestine. [12]

7) Trichilia emetica

This study demonstrated that extract with flavonoid rich fractions from Trichilia emetica possessed marked anti amylase activity which may be due to the presence of certain secondary metabolites. In particular, flavonoids are responsible for variety of pharmacological activities. [13]

3. SAPONIN AND HYPERGLYCEMIA

Diabetes mellitus is characterized by hyperglycemia which leads to oxidative stress and antioxidant defenses. Reactive Oxygen Species (ROS) directly oxidize and damage DNA, protein and lipids which play key role in the pathogenesis of late diabetic complications. Hyperglycemia activates several well characterized biochemical pathways like

i. Advanced glycation end products (AGES)

ii. Protein Kinase C (PKC)

iii. Polyol pathway

That play significant role in the cause of diabetic complications. Ability of saponin to reduce elevated plasma blood glucose makes saponin an excellent candidate in the treatment of diabetes mellitus. [14]

The hypoglycemic action of saponin is through a. Restoration of insulin response

b. Improvement in insulin signaling

c. Increase plasma insulin levels and induction of insulin release from the pancreas

d. Inhibition of diasaccharide activity e. Activation of glycogen synthesis

f. Inhibition of gluconeogenesis

g. Inhibition of α- glucosidase activity

h. Inhibition of mRNA expression of glycogen phosphorylase and glucose 6 phosphatase

i. Increase the expression of Glut4. [14]

3.1 Hypoglycemic potential of saponins

1) Anabasis articulate saponin

Saponin from areal parts of A.articulate showed potent glycemic control and prevent metabolic disorders and liver damage caused by hyperglycemia in streptozotocin induced diabetic hepatopathy in rats. The anti-hyperglycemic activit was attributed to the ability of saponin to induce the release of insulin from the pancreas. [15]

2) Astragalus membranaceus saponin

Astragalus saponin I, extracted from the root of Astragalus membranaceus has been reported to have various biological activities like increase in the secretion of insulin and C-peptide on rats. [16] Therapeutic effects on several pharmacological targets, such as oxidative stress, advanced glycation end products (AGEs), transforming growth factor β1 (TGF β1), in the development of Diabetic nephropathy and is a potential drug for prevention of early Diabetic nephropathy [17-18]. Astragaloside IV is a glycoside of cycloartane type triterpene saponin isolated from the plant, this saponin has been shown to possess many pharmacological activities including anti diabetes [18]. It also showed protective effect against the progression of peripheral neuropathy in STZ- induced diabetic rats. [19] The anti-diabetic mechanism of this compound is through a decrease in blood glucose concentration and an increase in plasma insulin levels. In another study, Astragaloside IV at 25 and 50 mg/ kg was reported to significantly decrease blood glucose, triglyceride and insulin levels, and inhibited the mRNA and protein expression as well as enzyme activity of glycogen phosphorylase and glucose 6 -phosphatase in diabetic mice. [20]

3) Dioscorea polygonoides saponin

A 1% inclusion of steroidal saponin from Dioscorea polygonoides in the diet of male diabetic rats for three weeks significantly decreased plasma glucose and reduced the activity of glucose 6- phosphatase in the liver. [21]

4) Dioscorea rotundata (Yam) saponin

Diosgenin is a hydrolysate of dioscin contained in the rootstock of Yam. It is a steroidal saponin, with many biological activities. Consumption of diosgenin demonstrated that it possessed hypoglycemic effect. One

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property of this saponin that is beneficial in diabetes is reduction of intestinal diasaccharide activities. Saponin from yam reduced intestinal sucrase activity in experimental studies in diabetic male wistar rats. The activity of glucose 6- phosphate was also significantly increased. [22-23]

5) Entada phaseoloides saponin

Saponin is very abundant in the seed of Entada phaseoloides. Saponin from the seed of E. phaseloides significantly reduced fasted blood glucose, serum insulin levels and alleviates hyperglycemia associated oxidative stress in type 2 DM rats. The observed effect of saponin implied that it exhibit its hypoglycemic effect through improving peripheral insulin resistance rather than protecting pancreas islet β- cells and stimulating insulin secretion.[24]

6) Garcinia kola root saponin

The findings indicated that administration of saponin from G. kola in alloxan induced diabetic rats caused significant anti hyperglycemic effect. The saponin extracted from the root of Garcinia kola led to a decrease of about 35.98% in blood glucose as against 31.26% for metformin after 3 days treatment. The capacity of saponin extracted from the root of G.kola significantly decrease elevated blood glucose levels to almost normal levels is an essential trigger for the liver to return toits normal homeostasis in experimental diabetic rats. Moreover, this fact indirectly indicates that the anti-diabetic effect of saponin from the root of Garcinia kola is partly due to insulin release from the existing cells of the pancreas. [25]

7) Helicteres isora saponin

Saponin from H.isora caused a significant reduction in the serum lipid, glucose levels, reduced the expression of fatty acid binding protein 4 (FABP4) and glucose 6-phosphatase while they increased the expression of adipsin, a peroxisome proliferator- activated receptors (PPAR) and glucose transprter 4 (Glut4). [26]

8) Ilex paraguariensis saponin

Saponin from Ilex paraguariensis caused a reduction in both visceral fat weight and glucose oxidation of hepatic and adipose tissue and significantly lower blood triglycerides level making saponin a potential anti-obesity agent. [27]

9) Momordica charantia saponin

Saponin from M. charantia also inhibited diasaccharide activity and elevation of blood glucose level after glucose loading and inhibit pancreatic lipase activity. [28] The AMP- activated protein kinase activation activity of this saponin was greater than that of troglitazone, a thiazolidinedione type anti diabetic drug. [29]

10) Panax notoginseng (PNS) saponin

Saponins from Panax notoginseng significantly improved glucose homeostasis and reduced fasting blood glucose levels in KK- Ay mice. Serum insulin levels or insulin resistance index decreased after treatment with PNS. PNS also enhanced insulin stimulated glucose uptake and glycogen synthesis in adipocytes. [30]

11) Polygonatum odoratum saponin

Saponin rich fraction obtained from P.odoratum showed potent anti-diabetic potential and glucose uptake in HepG2 cells. Saponin significantly ameliorated clinical symptoms of diabetes such as elevated blood glucose, body weight loss and increase food and water intake in streptozotocin (STZ) induced diabetic rats. Also an increase in superoxide dismutase (SOD) activity and decrease malondialdehyde (MDA) level in rat plasma was observed with saponin administration. Additionally, saponin rich fraction showed α- glycosidase inhibitory activity. [31]

12) Solanum anguivi saponin

Saponin from S.anguivi has the capacity to lower glucose level without weight gain in alloxan induced diabetic rats by restoring insulin response and induction of antioxidant enzymes inhibited by alloxan. [32]

13) Terminalia arjuna saponin

Arjunolic acid is a triterpenoid saponin that was first isolated from T. arjuna. Arjunolic acid showed potent anti-diabetic activity through inhibition of excessive ROS formation, α- amylase and α- glucosidase inhibitory activity, Down regulating the activation of phospho- ERK, phospho- p38, NF-KB and mitochondrial dependent signal transduction pathways by STZ leading to apoptotic cell death. [33]

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