Review Article

Salacia – The new multi-targeted approach in diabetics

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Abstract

Salacia species plant has been used traditionally as an Ayurvedic medicine for diabetes mellitus. Studies over the past decades have shown its multi-targeted role in diabetics. In the present review article, various mechanisms of action of *Salacia* on diabetics are discussed in detail. Apart from the well-known action of decreasing postprandial glucose sugar by inhibiting α-glucosidase and α-pancreatic amylase, it also inhibits aldose reductase which otherwise results in microvascular complications. Importantly, its peroxisome proliferator-activated receptor (PPAR)-γ agonist (such as thiazolidinediones, the insulin sensitizers) action increases the uptake of free fatty acid (FFA) and facilitates their storage in subcutaneous fat rather than the visceral fat. This reduces plasma FFA and insulin resistance. Furthermore, it increases the expression of and translocation to the cell surface of glucose transporter 1 and 4 receptors which result in glucose uptake by the liver and skeletal muscle and decreases plasma glucose levels. It also decreases inflammatory cytokines and increases adiponectin expression. *Salacia* as PPAR-α agonist (such as fibrates) has a role in the management of dyslipidemia. The activation of PPAR-α leads to the increased expression of lipoprotein lipase and apolipoprotein (Apo) A-V and decrease in hepatic Apo-C-III. These actions lower plasma triglycerides in chylomicrons and very low-density lipoprotein particles, thus liberating fatty acids, which are taken up and stored as fat in adipocytes. *Salacia* has been shown to suppress the overexpression of cardiac PPAR-α (similar to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) and thereby preventing diabetic cardiomyopathy. It also suppresses the cardiac angiotensin II Type 1 receptors resulting in antihypertrophic and antifibrogenic effect.

Keywords: Diabetes mellitus, mechanisms of action, peroxisome proliferator-activated receptor, *Salacia*

Introduction

Diabetes mellitus (DM), as we know, is a heterogeneous disorder with an interplay of genetics, environmental factors, insulin response to glucose, and vascular disease. There is heterogeneity in its various types too, for example, juvenile-onset diabetes, maturity-onset diabetes in young, and maturity-onset diabetes. The gold standard of treatment of DM is multifactorial therapy as the current consensus. The degree of relative risk of reduction with each individual risk factor target ranges from small for hyperglycemic lowering using oral hypoglycemic agent or insulin in the United Kingdom Prospective Diabetes Study, to moderate (example 10% with aspirin therapy), to substantial 25–30% with blood pressure and lipid lowering.

Here, in the present review article, various mechanisms of action of *Salacia* species on diabetics is discussed. *Salacia* species belongs to *Hippocastanaceae* family. Its biological property is concerted in its roots and leaves. It is reported that only 18 species of *Salacia* are identified in India and only five species are traceable, namely, *Salacia oblonga*, *Salacia chinensis*, *Salacia reticulata*, *Salacia roxburghii*, and *Salacia grandiflora*.

Observations

Many studies have reported the compounds salacinol, kotalanol, and kotalagenin 16-acetate which are found in the root of *S. oblonga*.[1,2] The hot water extract of *S. oblonga* (the yield from the dried root: 6.5%) contained 1.4%[3] or 0.74% of mangiferin, as mangiferin is an important component in various *Salacia* species (*S. oblonga*, *S. reticulata*, *S. chinensis*, and *Salacia prinoides*), The quantitative high-performance liquid chromatography analysis of mangiferin has been suggested as a suitable quality control of *Salacia* species and their products.[4-6]

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Dubey and his coworkers at Banaras Hindu University (1994 onward), Thanjavur, and SRM College, Chennai, have evaluated role of *S. oblonga*, *S. chinensis*, and *S. reticulata* as antidiabetic, in the management of diabetic microvascular complications, as hypolipidemic, antiatherogenic, antioxidant, anti-inflammatory, and anti-obesity agent. The pharmacological actions of *Salacia* are enumerated as below.

Salacia's antifibrotic and anti-arrhythmic action by suppressing cardiac angiotensin II signaling Type 1 receptors

The cardiovascular diseases (CVDs) such as arterial hypertension and left ventricular failure (systolic/diastolic) cause a pressure overload which causes mechanical stress which leads to the myocardial generation of angiotensin II. Two major classes of angiotensin II receptors have been described. Activation of the angiotensin II Type 1 (AT-1) receptors induces a cascade of phosphorylations that activate so-called mitogen-activated protein (MAP) kinases, which stimulate proliferation of fibroblasts, cellular hypertrophy, and apoptosis. The activation of angiotensin II Type 2 (AT-2) receptors inhibits MAP kinases via activation of different phosphatases. Thus, activation of AT-2 receptors has anti proliferative effects and supports cell survival.

Thus, inhibition of atrial angiotensin II-dependent effects by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduces the degree of atrial fibrosis, and thereby the inducibility of atrial fibrillation. Besides the proarrhythmic effects of angiotensin II in the atria, angiotensin II increases transmural dispersion of refractoriness in the ventricles.

S. oblonga root extract studies showed that it inhibited cardiac hypertrophy in Zucker diabetic fatty (ZDF) rats.[7-9] In addition, *S. oblonga* root extract diminished cardiac fibrosis in ZDF rats.[3] Moreover, *S. oblonga* root extract suppressed angiotensin II-stimulated hypertrophic response and protein synthesis in heart-derived H9c2 cells and angiotensin II-accelerated hyperplasia in rat cardiac fibroblasts.[7-9] These results suggest that *S. oblonga* root extract diminishes cardiac hypertrophy by decreasing the excessive collagen accumulation and the enlargement of cardiomyocytes.

Suppression of overexpression of cardiac peroxisome proliferator-activated receptor-α in diabetic heart

In the "idiopathic diabetic cardiomyopathy," which seems to be independent of risk factors of hypertension, dyslipidemia, etc., it has been postulated that abnormalities in myocardial energy metabolism play the causative role. A healthy heart displays tremendous metabolic flexibility; however, in insulin resistant and diabetic heart, the primary source of adenosine triphosphate (ATP) is fatty acid oxidation (FAO).[2] Uncontrolled, high-level FAO and impaired glucose utilization may have detrimental effects on cardiac structure and function by a variety of mechanisms.[10]

Cardiac metabolism is transcriptionally regulated by the peroxisome proliferator-activated receptor (PPAR)-α family of ligand-activated transcription factors. However, the cardiac over expression of PPAR-α in diabetics induces fatty acid accumulation in the heart,[11] which causes cardiac dysfunction.

There is emerging evidence that the PPAR-α/PPAR-γ coactivator 1 (PGC-1α) complex is activated in the diabetic heart. The myocardial expression of several PPAR-α target genes involved in fatty acid utilization was induced by both insulin-deficient and obese Type 2 diabetic mice.[12,13] When PPAR-α null mice were rendered insulin-deficient, the induction of PPAR target genes was markedly blunted.[12,13] The activation of PPAR-α by diabetes is consistent with increased availability of fatty acids, which serve as endogenous ligands for PPAR-α.

PPAR-α over expression induces expression of many genes involved in fatty acid catabolic pathways.[14] PPAR-α agonists also exhibit anti-inflammatory effect.[15] Huang *et al*. demonstrated that *S. oblonga* root extract, besides affecting circulating lipids, also reduced excessive cardiac triglyceride and none sterified free fatty acid (FFA) contents in ZDF rats.[7-9] Furthermore, the extract suppressed upregulated cardiac PPAR-α messenger RNA (mRNA) and protein expression, as well as cardiac over expression of carnitine palmitoyl transferase-1 (CPT-1) and acyl-CoA oxidase (AcO) mRNAs in ZDF rats though it did not affect cardiac PPAR-γ and PPAR-β/δ mRNA in ZDF rats.[7-9] This study showed that *S. oblonga* root extract inhibited the overexpression of cardiac fatty acid transport protein mRNA and protein and 5-AMP-activated protein kinase α2 mRNA and restored the down regulated cardiac acetyl-CoA carboxylase mRNA expression in ZDF rats.[7-9]

Salacia as peroxisome proliferator-activated receptor-γ agonist in diabetes mellitus and insulin resistance

Agonists of PPAR-γ are currently used therapeutically, especially in Type 2 DM, the thiazolidinediones, to influence FFA flux and thus reduce insulin resistance and blood glucose levels. This improves insulin action in peripheral tissues, attenuates hyper insulinemia, and lowers circulating levels of lipids. PPAR-γ agonists are highly expressed in adipocytes and mediate their differentiation. A major mechanism of the insulin-sensitizing action of PPAR-γ agonists results from the lowering of lipid supply to muscle and liver through a "lipid-stealing" by PPAR-γ-mediated effects in adipose tissue.[16,17] Activation of PPARs leads to the formation of heterodimers with retinoid-X receptors. In general, PPAR-α regulates genes involved in fatty acid uptake and oxidation, inflammation, and vascular function, whereas PPAR-γ regulates genes involved in fatty acid uptake and storage, inflammation, and glucose homeostasis. PPAR-δ regulates genes involved in fatty acid metabolism, inflammation, and macrophage lipid homeostasis.

Unlike PPAR-γ, PPAR-α mediates expression of genes regulating lipid oxidation.[16] PPAR-α agonists, such as fibrates, have been used to treat hyper triglyceridemia and reduce cardiovascular risk.[18] A number of studies in insulin-resistant

animal models have shown marked decreases in liver triglyceride content and adiposity by PPAR-α agonists.[19] There are also opposite reports that PPAR-α deficiency may even protect insulin sensitivity.[20] These data suggest that other factors, such as PPAR-γ responsive adipokines, may be involved in the insulin-sensitizing action of PPAR-γ agonists. Currently, there is enormous interest in the potential of combined PPAR-α/γ agonists for enhancement of insulin action together with reductions in tissue lipid accumulation and central adiposity.[21]

Currently, there is a lot of interest in synthetic ligand for PPAR-γ to treat patients with Type 2 diabetes as this have direct effect on lipid metabolism in adipose tissue and secondary effect on lipid and glucose metabolism in the liver and skeletal muscle.[22,23] PPAR-γ increases the uptake of FFA and their storage in subcutaneous fat rather than visceral fat. This reduced plasma FFA reduces insulin resistance. In addition, it increases the expression of and translocation to the cell surface of glucose transporter 1 and 4 receptors which result in glucose uptake by liver and skeletal muscle and decreases plasma glucose levels.[24] They also decrease inflammatory cytokines and increase adiponectin expression.[25]

Salacia as peroxisome proliferator-activated receptor-α agonist in the management of dyslipidemia

PPAR-α increases FAO in the liver, heart, kidney, and skeletal muscle. The activation of PPAR-α leads to the increased expression of lipoprotein lipase and apolipoprotein (Apo) A-V and decreased in hepatic Apo-C-III. These actions lower plasma triglycerides in chylomicrons and very low-density lipoprotein (LDL) particles, thus liberating fatty acids, which are taken up and stored as fat in adipocytes or for metabolism in skeletal muscle.[26] In addition, PPAR-α activation increases hepatic ApoA-I and II expression, which raises high-density lipoprotein (HDL) cholesterol levels, and promotes HDL-mediated cholesterol efflux from macrophages by inducing ATP-binding cassette A1 transporter.[27] In addition to the efficacy of fibrates in the clinical management of atherogenic dyslipidemias involving reduced HDL cholesterol and elevated triacylglycerol-rich lipoprotein levels, they are effective in shifting the LDL subclass distribution toward larger particle species.[28] Evidence of their beneficial effect on CVD has been obtained from several large clinical trials.[29]

A study in ZDF rats showed that the extract from *S. oblonga* root decreases plasma triglyceride and nonesterified fatty acid and the ratio of fatty droplets to total tissue in the liver.[7-9] The extract-enhanced PPAR-α medicated lipogenic gene expression (PPAR-α mRNA and protein, CPT-1, and AcO) in the liver of ZDF rats.[7-9] *In vitro* study demonstrated that the extract-enhanced PPAR-α luciferase activity in cells of the HEK293 cell line transfected with PPAR-α reporter gene and increased lipoprotein lipase mRNA expression and enzyme activity in THP-1 differentiated macrophage cells in PPAR-α-dependent manner.[7-9] *S. oblonga* water extract was found to activate PPAR-α in human hepatoma-derived HepG2 cells as evidenced by the upregulation of PPAR-α and AcO mRNA expression. The above studies indicate that *S. oblonga* root extract improves circulating and hepatic lipid metabolism by activating PPAR-α.

S. oblonga root extract's compound mangiferin (1.4%) lowers blood lipids in Type 2 diabetic animals.[30] It specifically activates PPAR-α luciferase activity in human embryonic kidney cells and enhances PPAR-α-dependent lipoprotein lipase expression and activity in the THP-1 derived macrophage cell line.[7-9] Therefore, mangiferin is one of the components responsible for the PPAR-α activator properties of *S. oblonga* root extract.

Salacia inhibits α-glucosidase and decreases postprandial glucose

Alpha-glucosidase inhibitors are well suited to treat postprandial hyperglycemia, a common and serious problem faced by many people with Type 2 diabetes metabolism. Alpha-glucosidase inhibitors cause competitive, reversible inhibition of α-glucosidase enzyme. This enzyme is present in the brush border of small intestine and hydrolysis complex sugars into monosaccharides. Alpha-glucosidase inhibitors also cause a concomitant decrease in gastric inhibitory polypeptide and a rise in late postprandial plasma glucagon-like peptide 1 levels. In individuals with normal or impaired glucose tolerance with hyperinsulinemia, α-glucosidase inhibitors decrease hyperinsulinemia and improve insulin sensitivity. In Type 1 diabetic patients, α-glucosidase inhibitors can be used to reduce postprandial glycemic excursions and decrease postprandial hypoglycemia.

In a sucrose tolerance test on healthy human volunteers, pretreatment with the aqueous extract of *S. reticulata* before sucrose loading significantly suppressed postprandial hyperglycemia.[31] *S. oblonga* root extract lowered acute glycemia and insulinemia in patients with Type 2 diabetes after a high-carbohydrate meal.[32] In the laboratory, *S. oblonga* root extract reduced postprandial plasma glucose levels in nonfasted ZDF rats, whereas it had minimal effect in fasted rats.[6] The methanolic extracts of *S. reticulata* and *S. oblonga* stems and roots dose-dependently reduced the postprandial hyperglycemia induced by maltose, sucrose, or starch but not by glucose or lactose in rats.[1,2] Similarly, *S. oblonga* root extract markedly inhibited the increase in plasma glucose levels in sucrose-loaded rats, whereas it showed no effect in glucose-loaded rats.[3] *S. oblonga* root extract and mangiferin concentration-dependently inhibited α-glucosidase activity *in vitro*.[29] Aqueous extract of *S. reticulata* strongly inhibited the activities of α-glucosidase and α-amyalse but not that of β-glucosidase. *S. chinensis* also showed α-glucosidase inhibitory activity.[4-6] Salacinol, kotalanol, and kotalagenin 16-acetate showed a stronger inhibition of the increased serum glucose levels in maltose and sucrose-loaded rats than acarbose.[1,2,33] The antidiabetic property of *Salacia* can be attributed to intestinal α-glucosidase inhibitory activity.

Salacia inhibits aldose reductase

Experiments in diabetic animals have implicated sorbitol accumulation in the development of cataracts. The use of aldose reductase inhibitors has shown in animal studies that diabetic complications, example cataracts, nephropathy, and slowing of nerve conduction, can be ameliorated. Aldose reductase is present in the lens, retina, Schwann cells of peripheral nerves, placenta, and red blood cells.

In diabetics, the glucose flux through the polyol pathway (which converts glucose to sorbitol) due to chronic hyperglycemia is significantly increased which is believed to be responsible for number of diabetic complications. A number of aldose reductase inhibitors in the management of diabetes are under trial. The crude methanolic extract and ethyl acetate soluble fractions of *S. oblonga* showed inhibitory activity on rat lens-derived aldose reductase.[1,2] Aqueous methanolic extract of *S. chinensis* also exhibited aldose reductase inhibitory activity.[4-6] The triterpenoids and diterpenoids isolated from ethyl acetate soluble fraction of *S. oblonga* extract showed inhibitory activity on rat lens aldose reductase while the water-soluble constituents showed little activity.[1,2] The extract of the stems of *S. reticulata* exhibited aldose reductase inhibitory activity, where mangiferin showed the most potent inhibitory activity.[4-6] These results warrant further investigation into the effect of *Salacia* on vascular and other complications of diabetes, as well as in ischemic injury of the heart.

Salacia inhibits-α pancreatic lipase

The hot water extract from the roots of *S. reticulata* suppressed pancreatic lipase activity, but it showed less effect on hormone-sensitive lipase activity in rat adipose tissue.[4-6] (-)-Epigallocatechin and (-)-epicatechin-(4b-8)-(-)-4-O-me thylepigallocatechin inhibited the pancreatic lipase activity with an inhibitory concentration 50% of 88 and 68 μg/ml, respectively.[4-6] Thus, inhibition of pancreatic lipase activity in the small intestine is suggested as one of the mechanisms of improvement of postprandial hyperlipidemia in Type 2 diabetes and obesity by *Salacia* root.

Discussion

S. oblonga root extract inhibited cardiac overexpression of AT-1 mRNA and protein,[7-9] as well as upregulating cardiac expression of transforming growth factor-β1 and -β3 mRNA in ZDF rats.[3] Taken together, these findings suggest that at least a part of the antihypertrophic and antifibrogenic effect of *S. oblonga* root extract occurs via a cardiac angiotensin II/AT-1 pathway. *S. oblonga* root extract reduces excess cardiac triglyceride accumulation and inhibits the increased myocardial FAO in the heart of the diabetic and the obese, by regulating at least in part cardiac PPAR-α mediated transcription of fatty acid metabolic genes. The studies indicated the link between myocardial energy metabolism and function. There is therefore a rationale for metabolic therapy to remedy cardiac hypertrophy and dysfunction in cardiac disease. The importance of the PPARs and PGC-1α in the control of cardiac energy metabolism makes these regulatory pathways attractive to be explored concerning the intricacies of modulating their activity for optimal therapeutic benefit. *Salacia* species have been extensively consumed in Japan, the United States, and other countries as a food supplement for the prevention of obesity and diabetes. Several reports from studies in animals have described hypoglycemic activity of *Salacia* species, including *S. oblonga,*[1,11,30,34] *S. reticulata,*[35,36] *S. prinoides* (syn. *S. chinensis*),[34] and *Salacia macrosperma*.[37] Further hypoglycemic activity of herbal preparations containing *Salacia* species have also been reported in human studies[37-40] Some toxicological studies have suggested minimal adverse effects of the herbal medicine in rodents.[41,42]

Conclusion and Future Research

One needs to investigate whether a dual PPAR-α/γ compound would exert additional beneficial effects on liver steatosis, adiposity, and insulin sensitivity compared with selective activation of PPAR-γ or PPAR-α. Although investigation of PPAR-δ has not yet progressed beyond the preclinical stage, these findings have led to suggestions that PPAR-δ may be a useful pharmacological target for treatment of obesity and insulin resistance. Furthermore, although the precise role of PPAR-δ in the inflammatory process has not been fully elucidated, this receptor may also have anti-inflammatory effects, in particular in macrophages. The effect of *S. oblonga* root extract on cardiac lipid metabolism, which was observed in ZDF rats, should be further examined that does it lead to improvement in cardiac function. In addition, the effect of *Salacia* root extract on PPAR-α-mediated transcription of fatty acid metabolism gene in adipose tissue, skeletal muscle, and kidneys needs to be seen.

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Conflicts of interest

There are no conflicts of interest.

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हिन्दी सारांश

सलेशिया - मधुमेह रोगियों की चिकित्सा में नवीन बहु-लक्षित प्रयोग

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मधुमेह की चिकित्सा के लिए सलेशिया प्रजाति के पौधों का उपयोग पारंपरिक रूप से आयुर्वेद में किया जाता है | पिछले दशकों में हुए अध्ययनों के आधार पर मधुमेह चिकित्सा में सलेशिया की बहु-लक्षित भूमिका सुनिश्चित हुई है| वर्तमान समीक्षा लेख में, मधुमेह रोगियों पर सलेशिया की विभिन्न प्रक्रियाओं के बारे में विस्तार से चर्चा की गई है | α-ग्लूकोसिडाज एवं α-पान्क्रियाटिक् अमाइलेज को कम करके भोजन के बाद ग्लूकोज कम करने के अलावा सलेशिया, आल्डोज रिडक्टेज की कार्मुकता को रोककर माईक्रो-वास्कुलार (सूक्ष्म कोशिकाओं) जन्य जटिल स्थितियों का निवारण करता है | इस के अलावा सलेशिया की और एक महत्वपूर्ण क्रिया यह है कि, इसकी पेरोक्सीसोम प्रोलाइफेरेटॉर-क्रियाशील संग्राहक (PPAR)-γ agonist (जैसे, इंसुलिन की ग्राही क्षमता को बढाने वाले थियाजोलीडाइनडिओनेस) की कारवाही से मुक्त वसा अम्ल का तेजी से ग्रहण हो जाता है और आंत वसा की तुलना में वसा में उनके संचय की सुविधा बढ जाती है। इस से इंसुलिन प्रतिरोध एवं प्लाज्मा मे स्थित मुक्त वसा अम्ल की मात्रा कम हो जाती है | इसके अतिरिक्त यह ग्लूकोसे ट्रांसपोरटेर 1 और 4 रिसेप्टर्स की कोशिका की सतह पर अभिव्यक्ति तथा स्थानांतरण की प्रक्रिया को बढ़ा देता है जिसके कारण यकृत और कंकाल की मांसपेशी द्वारा ग्लूकोज का अधिक उपयोग होता है, और इससे प्लाज्मा ग्लूकोज का स्तर कम हो जाता है | सलेशिया, सूजन के कारक जैसे साइटोकिन्स की मात्रा को कम करता है एवं अडिपोनेक्टिन की अभिव्यक्ति कराता है | सलेशिया में उपलब्ध PPAR-α agonist (जैसा कि फाइब्रेट्स मे देखा जाता है) रक्त मे स्थित वसा की मात्रा को कम करने मे सहायक सिद्ध हुआ है | इस प्रक्रिया के कारण काइलोमाइक्रोन में उपस्थित ट्राइग्लिसराइड की तथा निम्नघनत्व युक्त लिपो प्रोटीन की मात्रा कम होती है इसके फलस्वरूप वसा अम्ल का निष्कासन होता है जो कि परिणामतः ऑडिपोसाइट्स में चर्बी के रूप में संचित हो जाता है । सलेशिया कार्डियक पी पी ए आर – अल्फा (एंजियोटेन्सिन परिवर्तित किण्वक अवरोध / एंजियोटेन्सिन रिसेप्टर अवरोध समकक्ष है) के अधिक अभिव्यक्ति को रोकता है। जिससे कि मधुमेहजन्य कार्डियो मायोपैथी को रोका जा सकता है। यह कार्डियक एंजियोटेन्सिन II प्रकार के I रिसेप्टर को प्रतिरोधित करता है जिस कारण एंटीहाइपर ट्रोफिक तथा एंटिफाइब्रोजिन प्रभाव प्राप्त होता है।