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PLANT REVIEW

An Updated Review on the Phytochemistry, Pharmacology, and Clinical Trials of *Salacia oblonga*

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ABSTRACT

Salacia oblonga (*S. oblonga*), a perennial herb, has been used for thousands of years in ayurvedic medicine and is closely associated with prevention, treatment, and cure of various human ailments such as obesity and diabetes. A vast and wide range of chemical compounds such as polyphenols, friedelane-type triterpenes, norfriedelane-type triterpenes, eudesmane-type sesquiterpenes including various glycosides had been isolated from this plant. This review is aimed to survey the literature covering the phytochemistry and pharmacology of *S. oblonga* and to review the scientific data including active components and their multi-targeted mechanisms of action against various metabolic syndromes. We also included clinical trials related to this plant in this review. The overview would assist researchers to gather scientific information related to *S. oblonga* in future.

Key words: Clinical trials, pharmacology, phytochemistry, *Salacia oblonga*

INTRODUCTION

In the search for novel therapeutic molecules, the hybrid approach is to target multi-factorial diseases, especially metabolic syndrome. Natural products have been recognized as one of the major sources of hybrid molecules containing multi-structural units of a different class.[1] Continuous finding is necessary to find out multi-targeted therapeutics, which is helpful for newer drug discovery. To hit them, two strategies are adopted during discovery. Single compound is used to hit multiple targets which is the first approach and the second is to employ two or more active ingredients in a single drug.[2]

Salacia oblonga, commonly known as "ponkoranti" (Family: *Celastraceae*), due to its golden color root bark,[3] has been emerged to act as an active ingredient to hit multiple targets, preferably in case of all diabetic complications such as impaired glucose uptake, insulin resistance, dyslipidemia, cardiac complications, kidney disorder by acting through multiple targets either by the inhibition of α-glucosidase, aldose reductase (AR), pancreatic lipase, or by the activation of glucose transporter-4 (GLUT-4)-mediated glucose uptake, and various peroxisome proliferator-activated receptor (PPAR) subtypes.[4-8]

A plethora of research data indicates that numerous bioactive components from *S. oblonga* are potentially useful in the treatments of obesity, diabetes, and its complications. Several reports have described the hypoglycemic activity of *S. oblonga* in animals.[9,10] Furthermore, clinical trial had been performed using *S. oblonga* herbal preparation.[11-14] Again, no adverse effect was reported with *S. oblonga* extract (SOE) in rats, which supports a good safety potential in human.[15,16]

To date, despite the wealth of information available on the therapeutic importance of *S. oblonga* in literature, no review summarizes the real update on the molecular basis of biological activities and mechanisms of action of its active compound. Therefore, we surveyed research papers and clinical trials on *S. oblonga* and reviewed the scientific data, including active components and pharmacology. This review will provide the researchers with the current status of *S. oblonga* with a special emphasis on the regulation of hybrid approach of multiple molecular targets and their mechanism of action in diabetes, obesity, and their consequent complications, including various toxicological and cytogenetic aspects.

Phytochemistry

The phytoconstituents of *S. oblonga* are numerous, and they vary depending on the species to species and place of origin.[17] Kotalanol, kotalagenin 16-acetate, and salacinol were found in the root of *S. oblonga*.[7] *S. oblonga* hot water extract of root contains 1.4% of mangiferin (MA),[6] which was identified and quantified by high-performance liquid chromatography method. Apart from these unique constituents, the extract of *S. oblonga* has also been reported to contain neokotalanol,[18] ponkoranol,[19] neosalacinol, neoponkoranol,[18] 26-hydroxy-1,3-friedelanedione, 3 β,22α -dihydroxyolean-12-en-29-oic acid,[20] (-)-4-O-methylepigallocatechin,[21] salasol A,[22] salasol B, salasones A, salasones B, salasones C, salasones D, salasones E, salaquinone A, salaquinone B,[22,23] and 25,26-oxidofriedelane-1,3-dione.[24] All the chemical components of *S. oblonga* with their chemical structures are given in Figure 1.

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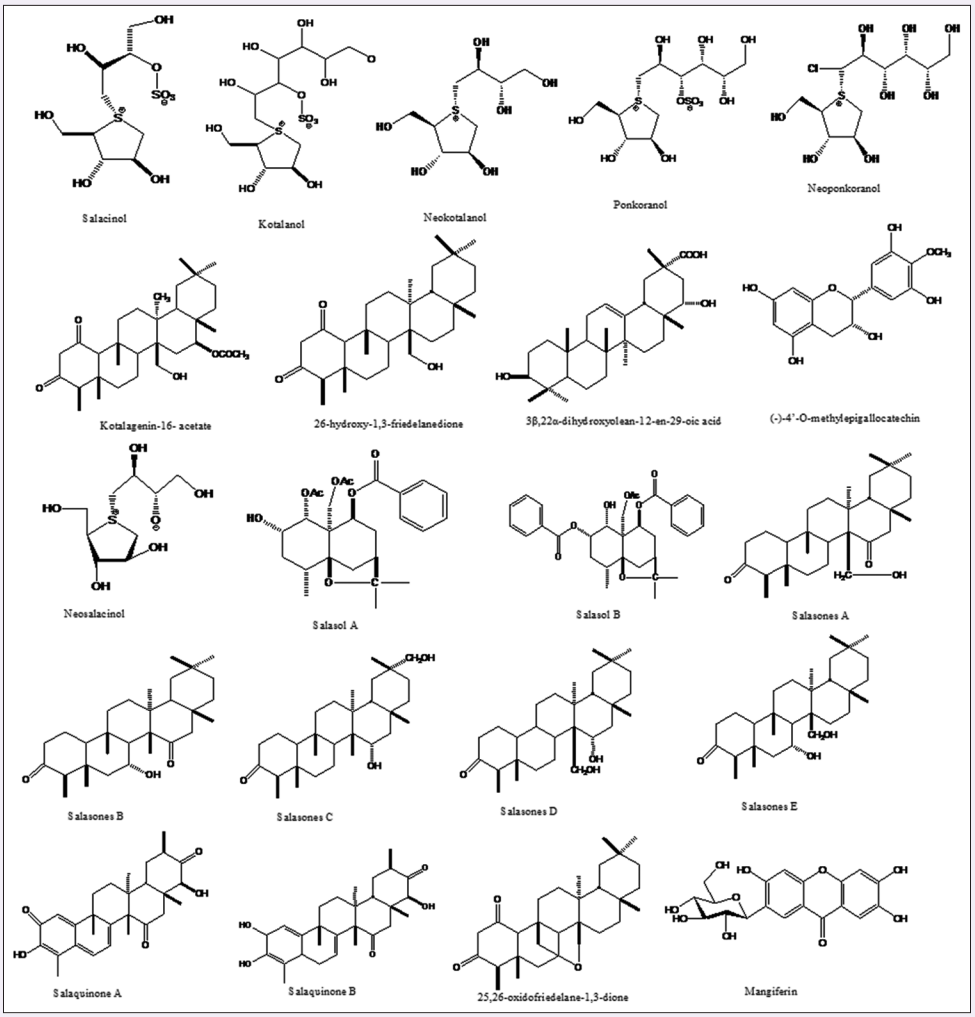

Figure 1: Important phytochemicals of *S. oblonga* participating in biological activities

Pharmacological Uses

The extract of *S. oblonga* has diverse local and traditional uses because of its action on different molecular targets in the human body. Herein, the different chemical constituents of the extract act on the different molecular targets owing to several useful biological activities which are summarized in Table 1.

Diabetes

Inhibition of α-glucosidase

Oxidative stress has an important contribution during diabetes propagation.[25] Numerous reports have documented that the reduction of antioxidant defenses is observed during an oral glucose challenge.[26,27] Glucose absorption delays during the inhibition of metabolic enzymes which suppresses postprandial hyperglycemia, resulting in improved glycemic control [Figure 2].[12] *S. oblonga* root (SOR) extract lowered glucose and increased insulin levels in patients with type 2 diabetes after meal.[28] The production of salacinol, kotalanol and kotalagenin-16-acetate maltose, sucrose, or starch was strong in rat plasma.[6,7,29,30]

In another experiment,[6] water extract of SOR containing MA was investigated against type 2 diabetes during cardiac fibrosis using obese Zucker rats, and the researchers demonstrated that SOR extract restored blood glucose level during cardiac fibrosis. It has also been demonstrated that MA showed much weaker effects than that of SOE having salacinol and kotalanol, suggesting that MA is a moderately active constituent for inhibiting α-glucosidase enzyme.[6]

Activation of glucose transporter 4-mediated glucose uptake

S. oblonga produced GLUT-4 activation through the inhibition of intestinal α-glycosidases and augmentation of glucose uptake in muscle and adipose tissues. Mangifrerin is the key constituent of SOE, which enhances 2-deoxy-D-glucose uptake by 50% in both L6-myotubes and 3T3-adipocytes. In addition, the effects are most likely mediated through two individual pathways that are linked to protein kinase and PPAR-γ activation.[4]

Inhibition of aldose reductase

Kotalagenin-16-acetate and MA had a dramatic role in AR inhibition which was observed in rats' lens-derived AR.[7,8] In another study, MA is reported to possess the onset or progression of diabetic complications including diabetic neuropathy and nephropathy.[31] These results further coined the protective effect of *S. oblonga* on vascular and other complications of diabetes.

Inhibition of nicotinamide adenine dinucleotide phosphate oxidase enzyme

During specified application,[32] *S. oblonga* demonstrated beneficial effects on mitochondrial localization in cells and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in glucose-induced rat

Table 1: Multi-targeted approach of biological activities

Molecular target	Action	Constituents	References
α-glucosidase	Inhibition of rat intestine-derived α-glucosidase activity *in vitro*	Salacinol, kotalanol	[7]
	Inhibition of yeast-derived α-glucosidase activity *in vitro*	Mangiferin	[6]
	Inhibition of N-terminal catalytic domain of intestinal human maltase glucoamylase	Kotalanol and its stereoisomer	[54]
GLUT-4 uptake	Stimulation of 2-deoxy-D-glucose uptake by 50% in both L6-myotubes and 3T3-adipocytes	Mangiferin	[4]
Aldose reductase	Inhibition of rat lens-derived aldose reductase activity *in vitro*	Mangiferin, salacinol, kotalanol, and kotalagenin 16-acetate	[7,8]
	Inhibition of aldose reductase activity	Various friedelanes	[45]
NADPH oxidase	Reduction of the amount of superoxide radicals by inhibiting NADPH oxidase enzyme in glucose-induced cytotoxicity on rat muscle cell line	Mangiferin and several other polyphenolic phytoconstituents	[32]
AT-1	Inhibition of angiotensin-II-stimulated [3H] thymidine incorporation by cardiac fibroblasts	Mangiferin	[5]
	Inhibition of angiotensin-II-induced ANP mRNA overexpression and protein synthesis in H9c2 cells	Mangiferin	[5]
Pancreatic lipase	Inhibition of porcine-derived pancreatic lipase activity *in vitro*	Mangiferin, salacinol, and (-)-4'-O-methylepigallocate-chin	[20]
PPAR-α	Activation of PPAR-α luciferase activity in HEK 293 cells	Mangiferin	[55]
	Activation of PPAR-α-dependent lipoprotein lipase expression and activity in the THP-1-derived macrophage cell line	Mangiferin	[55]
	Activation of PPAR-α in human hepatoma-derived HepG2 cells	SOW	[16]
	Activation of PPAR-α and lowering of triglyceride via hepatic mechanism	SOR	[56]
PPAR-γ	Stimulation of 2-deoxy-D-glucose uptake in L6-myotubes through PPAR-γ receptor	Mangiferin	[4]
SREBP-1/1c	Suppression of fructose-stimulated overexpression of SREBP-1/1c mRNA and inhibition of fructose-induced fatty liver	SOR	[57]
Insulin-mediated signaling	Activation of insulin-mediated signaling with multi-target pathways including GP, Akt/PKB, PTP1B, IR, the membrane G protein-coupled receptor, GR, α-amylase, α-glucosidase, 11β-HSDs, GAPDH, and G3PDH	PTs (friedelane and norfriedelane types)	[41-44,58]

PTs=Pentacyclic triterpenoids, GP=Glycogen phosphorylase, PKB=Protein kinase B, PTP1B=Protein tyrosine phosphatase 1B, IR=Insulin receptor, SOW=Water extract of *Salacia oblonga*, SOR=Root extract of *Salacia oblonga*, AT-1=Angiotensin-II type 1, GLUT-4=Glucose transporter-4, NADPH=Nicotinamide adenine dinucleotide phosphate, GR=Glucocorticoid receptor, 11β-HSDs=11β-hydroxysteroid dehydrogenase, GAPDH=Glyceraldehyde-3-phosphate dehydrogenase, G3PDH=Glycerol-3-phosphate dehydrogenase, PPAR=Peroxisome proliferator-activated receptor, SREBP=Sterol regulatory element-binding protein, ANP=Atrial natriuretic peptide, THP-1=Human monocytic cell line

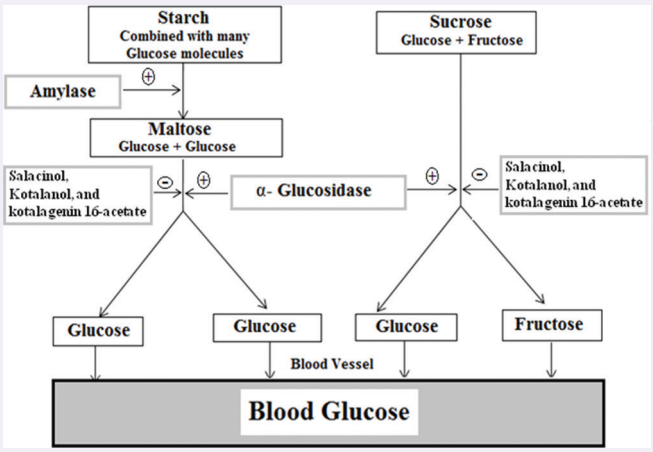

Figure 2: Function of intestinal α-glucosidase enzyme (positive circled sign shows activation and negative circled sign shows inhibition)

muscle cell line. In this study, the L6 cells were treated with high glucose in the absence or presence of SOE, and the NADPH oxidase enzyme activity was determined in cell lysates of control and treated groups.[33] NADPH oxidase enzyme activity was measured in terms of percentage of NADPH consumed in comparison to control. The data from this investigation suggested that high glucose concentration increased the oxidative stress in rat skeletal muscle cell line through the production of increasing amount of superoxide radicals by NADPH oxidase enzyme. Altogether, the study proved the antioxidant potential of SOE and indicated the possible involvement of skeletal muscle mitochondria in helping cells survive the stress.[32]

Inhibition of pancreatic lipase

SOE reduced plasma triglyceride level after loading olive oil in Zucker diabetic fatty (ZDF) rats, whereas it had no effect on plasma triglyceride in the fasted rats.[34] These results suggested that *S. oblonga* inhibited olive oil-induced hypertriglyceridemia by targeting the gastrointestinal system. The hot water extract of *S. oblonga* suppressed pancreatic lipase activity.[20] Therefore, the inhibition of pancreatic lipase activity in the small intestine was suggested as one of the main mechanisms of improvement of postprandial hyperlipidemia in type 2 diabetes and obesity by *Salacia* root.

Peroxisome proliferator-activated receptor-γ activator

PPAR-γ is a transcription factor predominantly expressed in adipose tissue, and it activates adipocyte differentiation both *in vivo* and *in vitro*.[35] When PPAR-γ is overexpressed, 3T3-L1 preadipocyte induction begins. This suggests that PPAR-γ suppression blocks adipogenesis and lipogenesis.[36] Thus, PPAR-γ agonism leads to the amelioration of lipid abnormalities in dyslipidemic patients. Findings from a number of

rodent studies have demonstrated that PPAR-γ agonists can improve insulin resistance, as well as dyslipidemia. Concomitantly, rodent disease models have demonstrated that PPAR-γ agonists prevented increased adiposity and body weight without any reduction in food intake.[37] An experiment showed that MA increases 2-deoxy-D-glucose uptake in both L6-myotubes and 3T3-adipocytes, and the effects are most likely to be mediated via two pathways, related to 5'-AMP-activated protein kinase and PPAR-γ and may be blocked by GW9662, an irreversible PPAR-γ antagonist.[4] *Salacia* species are also reported to inhibit PPAR-γ-mediated gene expression in 3T3-L1adipocytes.[38]

Activation of insulin-mediated signaling

Type 2 diabetes mellitus is a complex disorder in which the interaction between environmental and genetic factors results in the development of insulin resistance in peripheral tissues and β-cell dysfunction.[39,40] Among the various natural compounds, pentacyclic triterpenoids present in *S. oblonga* are a class of pharmacologically active and structurally rich metabolites with privileged motifs for further modifications, which are reported to act on glucose metabolism. Thus, it has become clear that PTs may exert their glucose-lowering effect through multi-target pathways, and these molecular targets include glycogen protein kinase B, protein tyrosine phosphatase 1B, insulin receptor, glucocorticoid receptor, phosphorylase, and the membrane G protein-coupled receptor (TGR5).[41] Therefore, oleane-, ursane-, and lupane-type triterpenes have been extensively studied.[42-45]

Cardioprotective action

Huang *et al*. found that SOE-treated ZDF rats showed less cardiac hypertrophy. SOE is used to suppress cardiac overexpression of atrial natriuretic peptide (ANP), brain natriuretic peptide, AT1 mRNAs, and angiotensin-1 (AT1) protein in ZDF rats. While SOE and MA suppressed angiotensin-II-induced ANP mRNA overexpression and protein synthesis in H9c2 cells. Their findings demonstrated that SOE decreases cardiac hypertrophy in ZDF rats, at least in part by inhibiting AT1 overexpression.[46]

Huang *et al*. suggested that SOE diminished cardiac hypertrophy by decreasing the excessive collagen accumulation and the enlargement of cardiomyocytes. Besides, AT1 also mediates the autocrine and paracrine effects of locally formed angiotensin-II which are believed to play a key role in the development of cardiac hypertrophy.[47] Furthermore, SOE also suppressed angiotensin-II-stimulated hypertrophic response and protein synthesis in heart-derived H9c2 cells and angiotensin-II-accelerated hyperplasia in rat cardiac fibroblasts.[5] Altogether, these findings suggest that at least a part of the anti-hypertrophic and anti-fibrogenic effects of SOE occur via a cardiac angiotensin-II type 1 receptor/AT1 pathway.

Anti-inflammatory activity

SOE had been shown to exhibit anti-inflammatory response by inhibiting the release of mediators of inflammation and or the stabilization of lysosomes. Recent studies demonstrated that an anti-inflammatory characteristic of SOE was observed on carrageenan and cotton plate-induced rat paw edema at the doses of 500, 1000, 1500, and 2000 mg/kg. The extract at 1000 mg/kg decreased the paw edema volume by 74.19% within 1 h after administration, while the standard drug hydrocortisone decreased the paw edema volume by 68.21% with respect to control.[48,49]

Anti-microbial activity

SOE was effective against Gram-positive (*Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Bacillus subtilis,* and *Listeria monocytogenes*) and Gram-negative bacteria (*Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Pseudomonas aeruginosa, Escherichia coli,* and *Salmonella typhimurium*) and fungus (*Aspergillus niger*). *S. oblonga* exhibited the highest activity against *K. pneumonia* than ethyl acetate extract in acidic media than neutral media. It is also used in the treatment of various bacterial infectious diseases such as gonorrhea, rheumatism, and skin diseases.[50]

Nephroprotective activity

Ethanol extracts of *S. oblonga* demonstrated protective activity against paracetamol-induced renal injury. The extract increased the level of anti-oxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and restored glutathione levels than paracetamol control groups.[51]

Anti-mutagenic activity

The hydroalcholic extract of root bark of *S. oblonga* had anti-mutagenic activity against mitomycin-C-induced testicular toxicity in albino Wistar rats. The measured parameters were sperm shape abnormality, sperm count, catalase, superoxide dismutase, and total protein. The results suggested that sperm shape abnormality and sperm count were restored to normal level at 1 g/kg of dose of extract. The enzyme levels also increased during the experiment, and the total protein level was similar to normal control.[52]

Weight loss

S. oblonga promoted weight loss via increasing the activities of cholecystokinin and glucagon-like peptide-1 at 1000 mg dose for 30 days. It also reduced the absorption of glucose by inhibiting the activity of oligonucleotides.[53]

CLINICAL TRIALS

The effects of SOE on postprandial glycemia and insulinemia were studied recently in 66 patients with type 2 diabetes in a randomized, double-blinded, crossover controlled trial. Each patient was administered with one of the three meals: A standard liquid control meal, a control meal + 240 mg SOE, and a control meal + 480 mg SOE. Both of the doses containing *Salacia* extract were found to be beneficial to this population for postprandial glucose control.[28]

The presence of SOE tends to lower postprandial glycemia and significantly reduce the postprandial insulin response. This result has been shown through repeated measurements of the effect of different doses of SOE on postprandial glycemic, insulinemic, and breath hydrogen responses in healthy adults through a double-masked, randomized, crossover design in 39 healthy, nondiabetic adults.[12]

Another clinical trial on a proprietary formulation Glucaffect™ was performed on 50 overweight patients in a single-blinded fashion. The rationale of the study was to prolong the satiety of overweight volunteers by providing delayed absorption of carbohydrates. Glucaffect™ provides potent α-glucosidase inhibitors of herbal sources such as French maritime pine bark extract Pycnogenol®, *Syzygium cumini* Madeglucyl™, and SOE. Consumption of Glucaffect™ enabled patients to lower blood-fasting glucose, body weight, and HbA1c levels as compared to the control group.[59]

In another randomized, double-masked, crossover design, 43 healthy controls were fed with one of the four meals: Control (a study beverage containing carbohydrate, protein, and fat), control + phenylalanine and leucine (AA), control + SOE, and control + SOE and AA. This clinical trial manifested the extract of *S. oblonga* as a promising nutraceutical ingredient for glycemic control, and supplementation with amino acids had no significant additional effect on glycemia.[11]

CONCLUSION

Prolonged exposure to high glucose concentration promotes the development of microvascular complications associated with diabetes mellitus. Such complications affect the kidneys (nephropathy), eyes (retinopathy), heart (cardiomyopathy), nerves (neuropathy), and blood vessels. Majority of the plants, except *S. oblonga*, used traditionally to cure diabetes have not been effective for the treatment of all diabetic complications. *S. oblonga* containing various active metabolites have been found to meet multiple targets to cure diabetes, obesity, and heart disease via inhibiting α-glucosidase, pancreatic lipase and AR, and modulating PPAR-α/γ-mediated lipogenic gene transcription, AT1 signaling, and GLUT-4-mediated glucose uptake. Although the multiple target regulatory activities of this unique ayurvedic medicine have been clearly shown to be of benefit, clinical trials are now crucial to evaluate the effectiveness and safety of *S. oblonga* in the treatment and prevention of these metabolic diseases in humans. In addition, further mechanistic studies are necessary to allow a better understanding of how the use of *S. oblonga* may interact with other therapeutic interventions. For the same reason, recently, there has been some excitement over the potential role of SOE.

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Conflicts of interest

There are no conflicts of interest.

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