**Salacia spp: Hypoglycemic Principles and Possible Role in Diabetes Management**

Amritpal Singh, MD Ayurveda; and Sanjiv Duggal, MSc

**Abstract**

The salacia species (Celastraceae), including *S chinensis*, *S reticulata*, and *S oblonga*, are used as antidiabetic agents in traditional systems of medicine such as Ayurveda and Unani. These plants have been used in India, Japan, and Korea to treat high blood glucose levels. Preclinical research and isolated clinical trials studying these effects have been promising. This review summarizes the pharmacological investigations of various species of salacia with respect to diabetes.

**Three salacia species—** *S chinensis*, *S reticulata*, and *S oblonga*—are used as antidiabetic agents in traditional systems of medicine such as Ayurveda and Unani. These plants have been used in India, Japan, and Korea to treat high blood glucose levels. Preclinical research and isolated clinical trials studying these effects have been promising. This review summarizes the pharmacological investigations of various species of salacia with respect to diabetes.

**Salacia chinensis** Linn; Syn: *S prinoides* DC

*Salacia chinensis* Linn is commonly studied among plants of the genus *Salacia*. It is commonly found in most of Asia as a climbing shrub, which grows up to 4 m tall. Branchlets are angular, with leaves carried on stalks 8 to 10 mm long. The leaf blade is elliptic, narrowly ovate-round, or obovate-elliptic. It has small yellow-green flowers with 3- to 6-flowered fascicles in a leaf axil. The berry is round or ovate, about 1 cm in diameter, red when ripe, and single seeded.

**Constituents**

Krishnan et al⁷ reported identifying proanthocyanidins from *S chinensis*. Morikawa et al⁸ reported new findings—3 new friedelane-type triterpenes named salasones A, B, and C; a new norfriedelane-type triterpene, salaquinone A; and a new acylated eudesmane-type sesquiterpene, salasol A—from the leaves of *S chinensis*. Zhang et al⁹ isolated 7 new megastigmane glycosides (foliasalaciosides E 1-3, F, G, H, and I) from the leaves of *S chinensis* collected in Thailand. Yoshikawa et al⁵ isolated new triterpene constituents, foliasalacins A(1)-A(4), B(1)-B(3), and C, from the leaves of *S chinensis*.

**Research**

In Ayurveda, the plant is known as *Saptchakra*. The plant is also used as a remedy for type 2 diabetes mellitus in the *Siddha* system of medicine. Sivaprasakam et al⁷ first reported a clinical study of an *S chinensis*-based formulation in diabetes mellitus. Kadal, a proprietary *Siddha* medicine composed of roots and bark of *S chinensis* and triphala (a combination of the fruits of *Terminalia chebula* Retz, *Terminalia belerica* Roxb, and *Emblica officinalis* Linn) were given to 25 patients with type 2 diabetes mellitus. Kadal was administered in a dose of 500 mg 2x/d, and triphala was administered at 2.5 g 3x/d with water for 4 months. The investigators reported that the formulation had a hypoglycemic effect.

Yoshikawa et al³ reported that a methanolic extract prepared from the stems of *S chinensis* had a potent antihyperglycemic effect in oral sucrose- or maltose-loaded rats. The extract also inhibited α-glucosidase and rat lens aldose reductase as well as nitric oxide production from lipopolysaccharide-activated mouse peritoneal macrophage and radical scavenging activities. Salacínol was identified as the α-glucosidase inhibitory principle of the extracts.

**Salacia reticulata** Wight

*S reticulata* is a climbing, perennial, woody plant that grows wild in southern India and northern Sri Lanka. It is a large, straggling, woody shrub with dichotomous branching. The bark is smooth, greenish grey, and thin, with white inside. Leaves are elliptic-oblung; flowers are bisexual, with 2 to 8 clustered in a leaf axil. There are 1 to 4 seeds, which have an almond-like shape. The roots and stems of *S reticulata* are used in Ayurveda to relieve dry mouth.

**Constituents**

Karunanayake et al⁵ isolated mangiferin from the root bark...
of *S reticulata*. Tezuka et al\textsuperscript{10} isolated a novel nortriterpenoid aldehyde, namely salacenonal. Yoshikawa et al\textsuperscript{11} isolated kotalanol, which was shown to have potential natural \(\alpha\)-glucosidase inhibiting activity, from the roots and stems of *S reticulata* through bioassay-guided separation. Kotalanol showed more potent inhibitory activity against sucrose than did either salacinol or acarbose.

Yoshikawa et al\textsuperscript{12} observed lipase inhibitory and lipolytic activities with mild antiobesity effects in rats using a hot-water-soluble extract from the roots of *S reticulata* and its polyphenolic constituents. Jayawardena and coworkers\textsuperscript{13} conducted a randomized, single-center, double-blind, crossover trial to study the efficacy of an herbal tea containing *S reticulata* (Kothala Himbutu tea) in 51 patients with type 2 diabetes mellitus. All participants had had type 2 diabetes mellitus for longer than 6 months, with evidence of stable glycemic control over the preceding 6 months (as assessed by HbA1c). They were randomized either to receive a standard preparation of Kothala Himbutu tea for 3 months followed by placebo in similar tea bags for a further 3 months (n=28) or to receive the tea and placebo in reverse order (n=23). All patients received detailed advice on diet, exercise, and lifestyle modification.

HbA1c was measured at recruitment, at 3 months, and on completion of the study at 6 months. Liver and renal functions were assessed biochemically at baseline and at 3 and 6 months, and adverse events were recorded. There were no significant differences between the 2 groups in age, body mass index, male/female ratio, glycemic control, or baseline laboratory tests. All differences between the 2 groups in age, body mass index, male/female ratio, glycemic control, or baseline laboratory tests. All patients completed both arms of the trial. The HbA1c at the end of drug treatment was significantly lower than after treatment with placebo.

Kishino et al\textsuperscript{14} reported that a mixture of the aqueous extract of *S reticulata* and cycloexetrin reduced the accumulation of visceral fat mass in mice and male Sprague Dawley rats. Ozaki and coworkers\textsuperscript{15} recently isolated a polyhydroxylated cyclic 13-membered sulfoxide from an aqueous extract of *S reticulata*. The \(\alpha\)-glucosidase inhibitory activity was much greater than the inhibitory activity of salacinol and kotalanol previously isolated from *S reticulata*. The same investigators also reported isolation and \(\alpha\)-glucosidase inhibitory activity of a novel 13-membered ring thiocyclitol from an aqueous extract of *S reticulata*. The inhibitory activity was investigated by maltose and sucrose loading on Wistar rats.

**Salacia oblonga** Wall

*S oblonga* grows in limited regions of India and Sri Lanka and is not yet well known in the United States. It is a small tree or climbing shrub found in rain forests. Leaves are ovate or ovate-lanceolate; flowers are greenish yellow and are found in short, congested cymes. Fruits are globose, about 3 cm in diameter, and are light brown or orange when ripe; there are 1 to 8 seeds imbedded in pulp. The roots and stems of *S oblonga* have been used extensively in Ayurveda and traditional Indian medicine for the treatment for diabetes. In Japan, the roots of the plant have been sold as a food supplement for several years.

Augusti et al\textsuperscript{17} reported 2 biologically active principles from petroleum ether extracted from the root bark of *S oblonga*. These 2 principles demonstrated about 60% and 76% of the hypoglycemic potency of an equal dose of tolbutamide (250 mg/kg) in albino rats.

Matsuda et al\textsuperscript{18} demonstrated that the aqueous methanolic extract of the roots of *S oblonga* inhibited the increase in serum glucose level in sucrose- and maltose-loaded rats. The watersoluble and ethyl acetate–soluble portions from the aqueous methanolic extract showed inhibitory activities on \(\alpha\)-glucosidase and aldose reductase, respectively. From the water-soluble portion, 2 potent \(\alpha\)-glucosidase inhibitors, salacinol and kotalanol, were isolated as well as 9 sugar-related components; a new friedelane-type triterpene, kotalagenin 16-acetate, was isolated from the ethyl acetate–soluble portion along with known diterpenes and triterpenes. The structure of kotalagenin 16-acetate was elucidated on the basis of physicochemical evidence. Principal components from this natural medicine were examined in terms of inhibitory activity on aldose reductase. The diterpene and triterpene constituents, including the new kotalagenin 16-acetate, were found to be responsible components for the inhibitory activity on aldose reductase.

Williams et al\textsuperscript{19} evaluated the effect of an herbal extract of *S oblonga* on postprandial glycemia and insulinaemia in patients with type 2 diabetes mellitus after ingestion of a high-carbohydrate meal. Sixty-six patients with diabetes participated in a randomized, double-blind, crossover study. In a fasted state, subjects consumed 1 of the following 3 meals: a standard liquid control meal, a control meal plus 240 mg *S oblonga* extract, or a control meal plus 480 mg *S oblonga* extract. Both doses of the salacia extract significantly lowered the postprandial positive area under the glucose curve (14% for the 240 mg extract and 22% for the 480 mg extract) and the adjusted peak glucose response (19% for the lower dose and 27% for the higher dose of extract) compared with the control meal. In addition, both doses of the salacia extract significantly decreased the postprandial insulin response, lowering both the positive area under the insulin curve and the adjusted peak insulin response (14% and 9%, respectively, for the 240 mg extract; 19% and 12%, respectively, for the 480 mg extract), compared with the control meal.

Huang et al\textsuperscript{20} investigated the effect of the water extract of *S oblonga* on obesity and diabetes-associated cardiac hypertrophy. They discussed the modulation of the cardiac angiotensin II type 1 receptor (AT1) expression in the effect. *S oblonga*, 100 mg/kg, was given orally to male Zucker diabetic fatty rats for 7 weeks. At the end of the study, the hearts and left ventricles were weighed, cardiomyocyte cross-sectional areas were measured, and cardiac gene profiles were analyzed. Angiotensin II–stimulated embryonic rat-heart–derived H9c2 cells and neonatal rat cardiac fibroblasts were pretreated with water extract of *S oblonga* and 1 of its prominent components, mangiferin, respectively. Atrial natriuretic peptide, mRNA expression, protein synthesis, and [\(^{3}H\)] thymidine incorporation were determined.

*S oblonga*–treated Zucker diabetic fatty rats showed less cardiac hypertrophy, as shown by a decrease in the weights of the hearts and left ventricles and by reduced cardiomyocyte cross-sectional areas. *S oblonga* treatment suppressed cardiac overexpression of atrial natriuretic peptide, brain natriuretic peptide, and aldose reductase.
peptide, AT1 mRNAs, and AT1 protein. Aqueous extract of S oblonga (50-100 µg/mL) and mangiferin (25 µmol) suppressed angiotensin II-induced ANP mRNA overexpression and protein synthesis in H9c2 cells. They also inhibited angiotensin II-stimulated [3H]thymidine incorporation by cardiac fibroblasts. The findings demonstrate that S oblonga decreased cardiac hypertrophy in Zucker diabetic fatty rats, at least in part by inhibiting cardiac AT1 overexpression.

**Salacia as a Peroxisome Proliferator-activated Receptor-α Activator**

Rong et al21 found that a water extract of S oblonga (100, 300, and 900 mg/kg/d by oral gavage), used over a 28-day period, elicited dose-related increases in liver weight by 1.6%, 13.4%, and 42.5%, respectively, and in the ratio of liver weight to body weight by 8.8%, 16.7%, and 40.2%, respectively, in male rats. These effects were less pronounced in female rats. Water extract of S oblonga selectivity increased liver mass in male rats but Sudan red staining was the same before and after, which indicates that hepatic lipid accumulation was similar in both genders. However, water extract of S oblonga even at the highest dosage did not influence serum alanine aminotransferase and aspartate aminotransferase activities of rats. Moreover, water extract of S oblonga was found to activate peroxisome proliferator-activated receptor-α (PPAR-α) and acyl-CoA oxidase mRNA expression. Thus, S oblonga-dependent PPAR-α activation may precede the development of the gender difference in hepatic hypertrophy.

**Toxicity**

**Reproductive Toxicity**

Ratnasooriya et al22 determined the effects of the S reticulata root extract on the reproductive outcome of normal Wistar rats (250-260 g) when administered orally (10 g/kg) during early days (1-7) and middays (7-14) pregnancy:

- The root extract significantly \((P<0.05)\) enhanced postimplantation loss (control vs treatment: early pregnancy, 4.7 ± 2.4% vs 49.3 ± 13%; midpregnancy, 4.7 ± 2.4 vs 41.7 ± 16%).
- Gestational length was unaltered, but the pups born had a low birth weight \((P<0.05)\); early pregnancy, 6.8 ± 0.1 vs 5.3 ± 0.1 g; midpregnancy, 6.8 ± 0.1 vs 5.0 ± 0.1 g) and low birth index \((P<0.05)\); early pregnancy, 95.2 ± 2.4 vs 50.7 ± 12.9%; midpregnancy, 95.2 ± 2.4 vs 58.3 ± 16.1%).
- Fetal survival ratio was low \((P<0.05)\); early pregnancy, 95.2 ± 2.4 vs 50.7 ± 12.9%; midpregnancy, 95.2 ± 2.4 vs 58.3 ± 16.1%.
- The viability index was also low \((P<0.05)\); early pregnancy, 94.9 ± 2.6 vs 49.5 ± 12.5%; midpregnancy, 94.9 ± 2.6 vs 57.1 ± 16.1%).

The investigators summarized that the S reticulata root extract can be hazardous to successful pregnancy in women. However, the root extract was nonteratogenic.

**Genotoxicity and Subchronic Toxicity**

Flammang et al23 investigated the genotoxicity of an S oblonga root extract using the standard battery of tests (reverse mutation assay; chromosomal aberrations assay; mouse micronucleus assay) recommended by the US Food and Drug Administration for food ingredients. S oblonga was determined not to be genotoxic under the conditions of the reverse mutation assay and mouse micronucleus assay and weakly positive for the chromosomal aberrations assay.

Continuing further studies, Flammang et al24 investigated the toxicity of an S oblonga root extract in a subchronic 90-day feeding study in rats. An in vivo—in vitro rat peripheral-blood lymphocyte chromosomal-aberrations assay was added at the end of the subchronic rat study to examine cultured lymphocytes for possible chromosomal aberration induction. The results indicated that aqueous extract of S oblonga was negative for the induction of chromosomal aberrations in cultured rat peripheral blood lymphocytes after 90 consecutive days of treatment. The no-observable-adverse-effect level was determined to be 2500 mg/kg/d, based on daily, oral, subchronic administration to rats.

**Dosages of Salacia-based Preparations**

Although no authentic information is available about dosages, a typical dose of salacia-based preparations is 2.5 to 5.0 g/d of the whole herb or a comparable amount as extract.

**Conclusion**

All 3 species of salacia have demonstrated α-glucosidase-inhibiting activity; acarbose, with salacinol and kotalanol, may be the active principles. The studies discussed above provide insights into the potential protective and antiobesity roles of salacia species. Some animal studies have demonstrated that salacia might have antidiabetic action similar to conventional PPAR-gamma activators. Clinical trials have also reported efficacy of salacia species in the treatment of diabetes mellitus. Toxicity data shows this herb does not have genotoxic and teratogenic effects but should be avoided during pregnancy.

**References**