

SALACIA RETICULATA WIGHT: A REVIEW OF BOTANY, PHYTOCHEMISTRY AND PHARMACOLOGY

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ABSTRACT

Salacia reticulata is a large woody climbing shrub naturally found in Sri Lanka and Southern region of India. It is widely used in treating diabetes, a chronic disorder in metabolism of carbohydrates, proteins and fat due to absolute or relative deficiency of insulin secretion with/without varying degree of insulin resistance. The decoction of *S. reticulata* roots is also used in the treatment of gonorrhea, rheumatism, skin diseases, haemorrhoids, itching and swelling, asthma, thirst, amenorrhea and dysmenorrhea. Presence of mangiferin (a xanthone from the roots), kotalanol and salacinol (from the roots and stems) have been identified as the antidiabetic principles of *S. reticulata*. Chemical constituents such as 1,3-diketones, dulcitol and leucopelargonidin, iguesterin, epicatechin, phlobatannin and glycosidal tannins, triterpenes, and 30-hydroxy-20(30) dihydroisoiguesterin, hydroxyferruginol, lambertic acid, kotalagenin 16-acetate, 26-hydroxy-1,3-friedelanedione, maytenfolic acid have also been detected in the roots of *S. reticulata*. The antidiabetic property of *Salacia* is basically attributed to the inhibitory activity of intestinal enzymes (α -glucosidase and α -amylase). Inhibition of intestinal enzymes delays glucose absorption into the blood and suppresses postprandial hyperglycemia, resulting in improved glycemic control. Furthermore, mangiferin has been reported to inhibit aldose reductase activity delaying the onset or progression of diabetic complications. Though diabetes has now become an epidemic affecting millions of people worldwide, neither insulin nor other modern pharmaceuticals has been shown to modify the course of diabetic complications mainly due to the multifactorial basis that involves both genetic and environmental risk factors. Therefore, effort is being devoted to find new therapeutics aimed at multiple targets, which has become a new paradigm in drug discovery. In this context, the discoveries on *S. reticulata* have lead to increase the consumption of the species across the world and it has now become a subject of broad studies for diabetes management.

Key words: *Salacia reticulata*, Mangiferin, Kotalanol, Salacinol, Diabetes

INTRODUCTION

Medicinal plants are an important element of the indigenous medical systems in Sri Lanka, where about 35 % of the population, even at present, depends on traditional systems of medical care (Smith *et al.* 2006). The Sri Lankans appeared to have developed a system whereby they select and continue to use plants that they find the most effective for health care purposes. Out of 1,414 medicinal plant species available in Sri Lanka, about 250 species are commonly used, while 50 species are heavily used (Pushpakumara *et al.* 2002). Despite the country is blessed with a rich diversity of medicinal plants, commercial exploitation of the important species is yet to be developed. Some of the long reputed Sri Lankan species have however been extensively investigated in other countries and subject of several publications even with no reference to Sri Lankan participation. The recent example of Kothala himbatu (*Salacia reticulata*), a species widely known for its antidiabetic properties has been investigated in Japan and the United States and patented (Pushpakumara *et al.* 2002). Though extensively investigated, it is unlikely that any

commercial exploitation of their discoveries will result in the sharing of benefits with Sri Lanka. Diabetes has now become an epidemic affecting millions of people worldwide. However, neither insulin nor other modern pharmaceuticals has been shown to modify the course of diabetic complications mainly due to the multifactorial basis that involves both genetic and environmental risk factors. Therefore, new therapeutics aimed at multiple targets have been extensively investigated. In this context, the discoveries on *S. reticulata* have lead to increase the consumption of the species across the world and it has now become a subject of broad studies for diabetes management. In order to meet the ever increasing demand, commercial exploitation of the species simultaneously with the scientific investigations is of paramount important. The present paper reviewed botany, uses, phytochemistry and pharmacology of Kothala himbatu (*S. reticulata*).

MEDICINAL PLANTS AND DIABETES

Diabetes is a chronic disorder in metabolism of carbohydrates, proteins and fat due to absolute or rela-

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tive deficiency of insulin secretion with/without varying degree of insulin resistance (Barar 2000; Yoshino *et al.* 2009). It has now become an epidemic affecting millions of people worldwide (Torben 2002) and the World Health Organization predicts that the number of people affecting diabetes may increase several fold in the near future. Diabetes can be defined as a disease where the body either produces little insulin/ceases to produce insulin, or becomes progressively resistant to its action (Ranjan and Ramanujam 2002). Therefore, the disease can be classified into two groups; type I (insulin-dependent) and type II (insulin-independent), which is more common accounting 90 % of the diabetic population (Yoshino *et al.* 2009). However, neither insulin nor other modern pharmaceuticals has been shown to modify the course of diabetic complications (Grover *et al.* 2002) mainly due to the multifactorial basis that involves both genetic and environmental risk factors (Kaplan and Junien 2000; Loktionov 2003; Reich and Lander 2001). Therefore, effort is being devoted to find new therapeutics aimed at multiple targets, which has become a new paradigm in drug discovery (Zhang 2005). In this context, it is of considerable interest to note that some natural products could act on multiple targets to influence multiple biological activities, producing significant physiological effects, and thereby providing benefits that cannot be obtained with a single compound (Yuhao *et al.* 2008).

Medicinal plants, since times immemorial, have been used in virtually all cultures in controlling and preventing diabetes. As per recent literature, more than 800 plants are reported to have antidiabetic properties (Eddouks and Maghrani 2004). Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity (Kesari *et al.* 2007). Hypoglycemic activity of herbal preparations containing *Salacia* species have been reported in many human studies (Collene *et al.* 2005; Heacock *et al.* 2005; Jayawardena *et al.* 2005; Kajimoto *et al.* 2000). The roots and stems of *S. reticulata* and the roots of *S. oblonga* have been extensively used for the treatment of rheumatism, gonorrhea, skin diseases, and particularly as a specific remedy for the initial stages of diabetes in the Ayurvedic system of traditional medicine (Matsuda *et al.* 2002; Yoshino *et al.* 2009). According to Kumar (2000), at least two Sri Lankan plants (*Salacia reticulata* and *Salacia prinoides*) being patented as having pharmaceutical potential in producing antidiabetic drugs. Recently, *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, as well as being

the subject of broad studies for diabetes management (He *et al.* 2009; Yuhao *et al.* 2008).

GEOGRAPHICAL DISTRIBUTION OF *SALACIA RETICULATA*

Salacia species (e.g. *S. oblonga*, *S. prinoides*, *S. reticulata*), known as 'Ponkoranti' in Ayurvedic medicine, are widely distributed in Sri Lanka, India, China, Vietnam, Malaysia, Indonesia and other Asian countries, where these species have been used for thousands of years in traditional medicines particularly for the treatment of diabetes (He *et al.* 2009; Yuhao *et al.* 2008). *S. reticulata* is known to be distributed in Sri Lanka and the Southern region of India (Matsuda *et al.* 2002). Though rare, this species could also be found in evergreen forests of Western Ghats (Ravikumar and Ved 2000). In Sri Lanka, *S. reticulata* is known to be found mainly in dry zone, which includes districts such as Hambanthota, Anuradapuraya, Pollonnaruwa, Monaragala, Kurunegala and Puttalm. However, documentary evidence is lacking on the precise locations in which the species is abundantly distributed.

BOTANICAL DESCRIPTION AND PROPAGATION

S. reticulata WIGHT (Sinhala: *Kothala himbatu*) is a large woody climbing shrub belongs to family Hippocrateaceae (Matsuda *et al.* 2002). The greenish grey color bark of the plant is smooth, with white inside. The average dimension of a leaf is 3 – 6 inches long and 1 – 2 inches broad (Sandhu and Singh 2005). They are opposite and elliptic-oblong, base acute, apex abruptly acuminate, margin toothed with minute rounded teeth, leathery, hairless, shiny, lateral nerves about seven pairs, prominent beneath. *S. reticulata* produces greenish white to greenish yellow color flowers as clustered (2-8) in leaf axils (Ravikumar and Ved 2000). Flowers are bisexual, calyx lobes entire, anthers dehiscing transversely. Fruits are globose, tubercular, pinkish orange when ripe. They contain 1 - 4 seeds (Ravikumar and Ved 2000, Subasinghe *et al.* 2008). The plant flowers in December under Indian conditions (Sandhu and Singh 2005), whereas in Sri Lanka, flowering starts in late November and seeds are available from March to June (Subasinghe *et al.* 2008).

A mature *S. reticulata* plant produces thousands of seeds per a season (Subasinghe *et al.* 2008). The species is generally believed to be regenerated only by means of seed propagation, however, *Kothala himbatu* could also be vegetatively propagated by means of stem cuttings (Subasinghe *et al.* 2008) and root cuttings (Oommen *et al.* 2000). Sand media was found to be good for seed germination in



Figure 1. *S. reticulata* fruiting branches with mature pods

which seeds complete germination within 21 – 30 days (Oommen *et al.* 2000). According to Subasinghe *et al.* (2008), de-pulped seeds soaked in cold water for 24 hrs should be sowed in coir dust media to get the highest germination. Seedlings should be transplanted into poly-bags and 2-3 months later they are ready for field establishment (Oommen *et al.* 2000).

Though a mature plant produces thousands of seeds per a season, the species is considered to be rare implying that the viability and/or germination ability of the seeds are poor. However, laboratory investigations have confirmed that high germination percentage can be obtained by sowing them in coir dust media after pre-soaking in cold water for 24 hrs. Therefore, poor regeneration capacity of the species might be attributed to the poor moisture availability of the soil at the time of seed maturity. Low survival ability of seedlings in a dry spell might be another possible reason for poor regeneration capacity.

USES

The decoction of *S. reticulata* roots is used in the treatment of itching and swelling, asthma, thirst, amenorrhea and dysmenorrhea (Tissera and Thabrew 2001). The roots are acrid, bitter, thermogenic, urinary, astringent, anodyne, anti-inflammatory (Nadkarni 1993). The roots and stem of *S. reticulata* have been widely used in treating diabetes and obesity (Im *et al.* 2008; Li *et al.* 2008), gonorrhea and rheumatism (Im *et al.* 2008), skin diseases (Im *et al.* 2008; Matsuda *et al.* 2002) and haemorrhoids (Nadkarni 1993). In addition, the water extracts of leaves of *S. reticulata* could be beneficial for the prevention of diabetes and obesity as its multiple effects such as the ability to increase the plasma insulin level and lower the lipid peroxide level of



Figure 2. *S. reticulata* rooted cutting

the kidney (Yoshino *et al.* 2009). In addition to the above, *S. reticulata* has been widely employed in traditional medicine for treating or preventing several other disorders, however, published information on such usages are lacking. It has been noticed that traditional practitioners appeared to have developed a system whereby they find the most effective parts of the plant for different health care purposes and continue to use them even without the proofs provided by standard clinical trials.

PHYTOCHEMISTRY

The constituents of *Salacia* are numerous and may vary depending on the species and place of origin (Yuhao *et al.* 2008). Presence of mangiferin ($C_{19}H_{18}O_{11}$), kotalanol ($C_{12}H_{24}O_{12}S_2^+$) and salacinol ($C_9H_{18}O_9S_2^+$) have been identified as the antidiabetic principles of *S. reticulata* through pharmacological studies (Yoshikawa *et al.* 1997, 1998; 2001). Other chemical constituents such as 1,3-diketones, dulcitol and leucopelargonidin (a linear iso-mer of natural rubber), iguesterin (quinonemethides), epicatechin, phlobatannin and glycosidal tannins, triterpenes, and 30-hydroxy-20(30) dihydroisoguesterin, hydroxyferruginol, lambertic acid, kotalagenin 16-acetate, 26-hydroxy-1,3-friedelanedione, maytenfolic acid have also been detected in the root of *S. reticulata* (Premakumara *et al.* 1992; Tissera and Thabrew 2001; Yoshikawa *et al.* 1997, 1998). Though the chemical composition of different parts of the plant has been extensively studied, a complete picture of as to how different active ingredients act on physiological processes of the human body is yet to be elaborated.

PHARMACOLOGY

Kajimoto *et al.* (2000) reported that a double-blind placebo-controlled study performed in Japan resulted in significantly decreased blood sugar levels in

humans with mild type II diabetes, receiving *S. reticulata* extract as part of their diet, as compared to control. In a sucrose tolerance test on human volunteers, pretreatment with the aqueous extract of *S. reticulata* prior to sucrose loading significantly suppressed postprandial hyperglycemia (Shimoda *et al.* 1998; Tanimura *et al.* 2005). Water extract prepared from *S. reticulata* leaves can also prevent diabetes and obesity similarly to that of roots and stems (Yoshino *et al.* 2009). Mangiferin, one of the main components in *Salacia* species (Li *et al.* 2004), has been reported to be potent α -glucosidase inhibitors that have been shown to inhibit increases in serum glucose levels (Yoshikawa *et al.* 1997, 1998, 2001). Aqueous extract of *S. reticulata* strongly inhibited the activities of α -glucosidase and α -amylase, but not that of β -glucosidase (Shimoda *et al.* 1998). *S. oblonga* root extract lowered acute glycemia and insulinemia in patients with type II diabetes after a high carbohydrate meal (Williams *et al.* 2007). *S. oblonga* root extract concentration-dependently inhibited α -glucosidase activity *in vitro* (Li *et al.* 2004). *S. chinensis* also showed α -glucosidase inhibitory activity (Yoshikawa *et al.* 2003). The intestinal enzymes α -glucosidase and α -amylase break down starches, dextrins, maltose and sucrose into absorbable monosaccharides, thus, it could be suggested that the antidiabetic property of *Salacia* is partially attributed to intestinal α -glucosidase inhibitory activity (Yuhao *et al.* 2008). Furthermore, inhibition of above enzymes delays glucose absorption into the blood and suppresses postprandial hyperglycemia, resulting in improved glycemic control (Heacock *et al.* 2005).

In addition, mangiferin can activate PPAR- α luciferase activity in human embryonic kidney 293 cells and enhances PPAR- α -dependent lipoprotein lipase expression and activity in the THP-1 derived macrophage cell line (Huang *et al.* 2006). This compound could also inhibit aldose reductase activity, thereby delaying the onset or progression of diabetic complications (Yoshikawa *et al.* 2001).

STUDIES WITH ANIMAL MODELS

Aqueous extract of *S. reticulata* stems administered to normal mice resulted in reduced obesity, thus potentially could reduce the risk of associated diseases including type II diabetes (Im *et al.* 2008). Experimentally, the root extract of *S. reticulata* has been found to have potent hypoglycemic activity both in normal (Tissera and Thabrew 2001), and in streptozotocin-induced diabetic rats (Serasinghe *et al.* 1990; Tissera and Thabrew 2001). A methanolic extracts of *S. reticulata* (50–200 mg/kg, per os) has strongly inhibited the increase in serum glucose level after administration of maltose or sucrose, but

not glucose, in rats (Matsuda *et al.* 2002). Furthermore, the extracts inhibited rat intestinal maltase and sucrase *in vitro*, although even at high doses the extracts did not have any effect on experimental hyperglycemia induced by injection of alloxan in mice (Matsuda *et al.* 2002). Mangiferin directly acts on liver cells and suppresses the gluconeogenic pathway resulting in decreased fasting blood glucose level in diabetes mice (Im *et al.* 2008). Salacinol, kotalanol and kotalagenin 16-acetate showed a stronger inhibition of the increased serum glucose levels in maltose and sucrose loaded rats (Matsuda *et al.* 1999, 2002). The methanolic extracts of *S. reticulata* stems and roots dose-dependently reduced the postprandial hyperglycemia induced by maltose, sucrose or starch, but not by glucose or lactose in rats (Shimoda *et al.* 1998; Matsuda *et al.* 1999, 2002). Serasinghe *et al.* (1990) orally administered an aqueous extract of *S. reticulata* prepared from the root bark to streptozotocin-induced diabetic rats and reported that the blood glucose lowering effects of *S. reticulata* was persistent (Serasinghe *et al.* 1990). Although the mechanism underlying the liver glucose production by *S. reticulata* is yet to be clarified, the observations described above suggested that the traditional antidiabetic property of this natural medicine is attributable to intestinal α -glucosidase inhibitory activity (Matsuda *et al.* 2002). Furthermore, it was reported that mangiferin lowers blood lipids in type II diabetic animals (Miura *et al.* 2001). This was further confirmed by Yoshikawa *et al.* (2002), as they observed that an aqueous extract of *S. reticulata* roots could suppress body weight gain and perirenal fat accumulation in female Zucker fatty rats.

SAFTY EVALUATION

The safety of the extracts of the *Salacia* species have been confirmed by the investigations on genotoxicity, subchronic toxicity etc (Wolf and Weisbrode 2003). Reverse mutation assay; chromosomal aberrations assay and mouse micronucleus assay were employed to evaluate the potential genotoxicity of *Salacia* root extract and no genotoxicity under the conditions of the reverse mutation assay and mouse micronucleus assay were found, but weakly positive for the chromosomal aberrations assay (Flammang *et al.* 2006). No deaths or abnormalities in gross pathological findings were observed from an oral single dose toxicity test conducted with rats and no cells with chromosomal aberrations were observed in a chromosomal aberration test using cultured mammalian cells (CHL/IU), suggesting that *S. reticulata* has no serious acute toxicity or mutagenicity (Shimoda *et al.* 1999). Furthermore, oral administration of the *S.*

reticulata root extract during early or mid-pregnancy had no effect on fertility in terms of uterine implants, implantation index or gestation index (Ratnasooriya *et al.*, 2003). However, as it may pose a considerable threat to successful pregnancy, use of the *S. reticulata* extract should be avoided by women with pregnancy complicated by diabetes (Ratnasooriya *et al.* 2003). Though many toxicological studies carried out with rodents have proved that little or no adverse effects of *S. reticulata*, clinical trials are crucial to further confirm the safety of the use of *Salacia* extracts. The research evidence suggests that this unique traditional medicine fulfills a multiple-target strategy in the prevention and treatment of diabetes and obesity. However, further mechanistic studies are needed to illustrate as to how different usage of *S. reticulata* interact with other therapeutic interventions.

CONCLUSION

The antidiabetic property of *Salacia reticulata* has been proved scientifically and it is basically attributed to the inhibitory activity of intestinal enzymes (α -glucosidase and α -amylase). Inhibition of intestinal enzymes delays glucose absorption into the blood and suppresses postprandial hyperglycemia, resulting in improved glycemic control. The findings have lead to increase the consumption of the species across the world and it has now become a subject of broad studies for diabetes management. Increasing demand, on the other hand, may create extra pressure on natural habitats. Thus systematic cultivation is needed in order to ensure the sustainable utilization and conservation of the species.

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