Review Article

A Comprehensive Review of *Salacia reticulata*: Botanical, Ethnomedicinal, Phytochemical, and Pharmacological Insights

ABSTRACT

Salacia reticulata (HIPPOCRATEACEAE) is a large ligneous climber or scandent shrub held by Sri Lanka, the Andaman Islands, and south India. It is known as Kothala himbutu/Himbutu wel in Sinhalese and is well-known among natives for its extensive use in diabetes treatment, a chronic condition impacting carbohydrate, protein, and fat metabolism due to insulin secretion deficiencies, with or without insulin resistance. It is also employed in remedies for various ailments, including asthma, amenorrhea, itching and other skin problems, gonorrhoea, haemorrhoids, swellings, and obesity. Key antidiabetic compounds within *S. reticulata* are recognized, such as salacinol and kotalanol (from both roots and stems), and mangiferin (root-derived). Additionally, the plant's roots contain diverse chemical constituents like 1,3-diketones, 26-hydroxy-1,3-friedelanedione, 30-hydroxy-20(30) dihydroisoiguesterin, dulcitol, epicatechin, glycosidal tannins, hydroxyferruginol, iguesterin, kotalagenin 16-acetate, lambertic acid, leucopelargonidin, phlobatannin, and triterpenes, collectively contributing to its therapeutic potential. Salacia's antidiabetic effects are considered to stem primarily from its capacity to inhibit intestinal enzymes, specifically α-glucosidase and α-amylase, delaying glucose absorption and enhancing blood sugar control. Furthermore, the Salacia extracts have appeared to be very safe *in vivo* and *in vitro* experiments, and human use. The purpose of the current study is to review the botanical, ethnomedicinal, phytochemical, and pharmacological data on *Salacia reticulata* while assessing the evidence pertaining to *in vitro*, animal, and human studies for its anti-inflammatory, antibacterial, anti-diabetic, anti-obesity, anti-oxidant, and anti-hyperlipidaemic effects.

Keywords: Salacia reticulata, Ethnomedicinal, Phytochemical, anti-diabetic, anti-obesity, Kothala himbutu,*Sri Lanka*

1. INTRODUCTION

Sri Lanka is very popular for its traditional medicinal systems and ancient healing practices with medicinal plants being a major element of them (1, 2, 3, 4). Despite the modern medicinal systems, herbal plants are still being used widely to treat illnesses (5, 6, 7). It is reported that nearly 35% of Sri Lankans still choose traditional medicinal systems for their medical care. There are about 1,414 medicinal plant species present in Sri Lanka. It is found that among them, around 250 species are commonly utilized while around 50 species are heavily involved (8, 9, 10). The present example of *Salacia reticulata* Wight (HIPPOCRATEACEAE), also known as Kothala himbutu/ Himbutu wel by Sinhalese is a valuable species extensively utilized for its anti-diabetic properties (11). Genus Salacia consists of around 120 species (e.g.,*Salacia prinoides*, *Salacia oblonga*, *Salacia reticulata*) and is distributed widely in Asian countries (12).*Salacia reticulata*is an enormousligneous climber or scandent shrub that is indigenous to Sri Lanka, the Andaman Islands, and some parts of Southern India (13, 14). In addition to treating diabetes, this plant is also involved in the treatment of asthma, amenorrhea, itching and other skin-related issues, gonorrhoea, haemorrhoids, swellings, and obesity. This valuable plant is found to be rich in important phytochemicals like mangiferin, kotalanol, and salacinolalong with numerous chemical constituents including 1, 3- diketones, iduesterin, epicatechin, and many more (15).

Extracts of Salaciashowseveral mechanisms of action related to the metabolism of carbohydrates and lipids, which is one of the reasons why interest in this plant has increased recently. Other factors include the need for safe yet effective medications that can help with the control of blood glucose and lipid levels and a dramatic rise in the prevalence of diabetes and early-onset diabetes (16).

Additionally, with respect to the research on animal models, humans, and *in vitro* experiments, the Salacia extracts have appeared to be free from adverse effects(12, 15, 16).

This present study aims to review the botanical, ethnomedicinal, phytochemical, and pharmacological information of *Salacia reticulata* while evaluating the evidence related to *in vitro*, *in vivo*, and human studies for its anti-inflammatory, antibacterial, anti-diabetic, anti-obesity, anti-oxidant, and anti-hyperlipidaemic effects.

Fig 1: Well-grown *Salacia reticulata*Wight, bearing fruits (15)

Fig 2: Habitat of the plant species (13)

Fig 3: A voucher specimen of *Salacia reticulata* Wight (14).

1.1 Taxonomic hierarchy and other names

1.1.1 Taxonomic Hierarchy(14)

Domain – Eukaryote

Kingdom - Plantae

Subarian - Tracheobionta

Super division - Spermatophyta

Division - Magnoliophyte

Class - Magnoliopsida

Subclass - Rosidae

Order - Celastrales

Family - Celastraceae

Subfamily - Salacioideae

Genus - Salacia

Species – *Salacia reticulta* Wight

1.1.2 Other names(13, 17)

Sinhala - Kothala himbutu/ Himbutu wel

Malayalam – Ekanayakam, Ponkoranthi, Koranti

Kannada – Ekanayakam

Tamil – Pronkoranthi, Kadalainjil

Telegu – Anukudu Cettu

Sanskrit – Vairi, Pitika

1.2 Geographical distribution

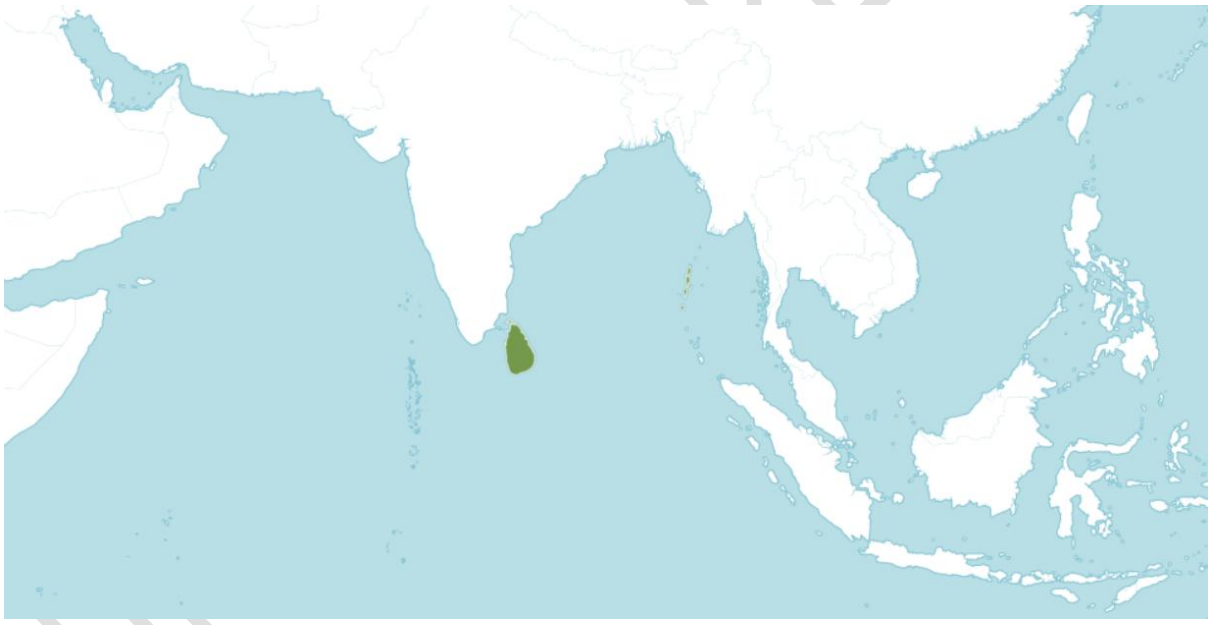


Fig 4 :The distribution of *Salacia reticulata* Wight (18)

The Andaman Islands and Sri Lanka are home to *Salacia reticulata*. In the dry zone of Sri Lanka, which includes the districts of Anuradhapura, Hambanthota, Kurunegala, Polonnaruwa, Puttalam, and Monaragala, it has a natural habitat of forests (14, 15). Apart from its native lands, the species can also be found in other Asian countries including China, India, Indonesia, Malaysia, and Vietnam (16, 19).

1.3 Botanical description and cultivation

S. reticulata is a woody, perennial climbing tree. The branching system is dichotomous. The bark is thin, smooth, greenish-grey, and internally white. The elliptic-oblong leaves are opposite in arrangement. Leaves are 4.2 – 11.6 × 2.2 – 5.4 cm in size and have small, rounded teeth along the margins, acute bases, and sharply pointed apexes. At the axis of the leaves, the bisexual flowers are

grouped in groups of 2-8. They are 6-7mm in diameter with 5 petals and range in colours from greenish-white to greenish-yellow. The edible fruit is tubercular and ranges from 1.6 – 3.8cm in diameter. When ripe, the globose drupe turns pink-orange in colour. There are 1-4 yellow-coloured almond-like seeds inside the fruits (13, 14).

Fig 5 :Fruits of *S. reticulata* (13)

Fig 6:Flowers of *S. reticulata* (18)

The plant starts to bloom near the close of November while seeds are present between March and June (20). In India, the flowering occurs in December (21). Like other members of its genus, *S. reticulata* is a climbing shrub that develops naturally in tropical areas. Thousands of speeds are produced by an adult plant each season (20). The species is typically thought to only be regenerated through propagation through stem-cutting (20) and root-cutting (22). Sand media was discovered to be effective in helping seed germinate completely in 21-30 days (22).

To achieve the highest germination, de-pulped seeds should be sown in coir dust media after soaking in cold water for 24 hours according to Subasinghe *et al*., 2008(20). According to Oommen *et al*., 2000, seedlings should be transplanted into polybags and prepared for field establishment after 2-3 months(22). Even though a mature plant can produce thousands of seeds per season, the fact that the species is rare suggests that the seeds have poor viability and/or germination abilities. It is assumed that the low moisture available on soil during the maturity period may be responsible for the poor regeneration capacity while poor capacity for survival during the dry season is another factor. This assumption is proven correct by laboratory tests showing that a high germination percentage results from pre-soaking the seeds for 24 hours before sowing seeds in coir dust media (15).

2. ETHNOMEDICINAL USES

It is common practice in traditional medical systems like "Ayurveda" to treat diabetes mellitus with a variety of herbal preparations in Sri Lanka. In Sri Lanka and other Asian nations, *S. reticulata* is widely used as a diabetes treatment. The preparation is typically consumed as herbal tea (Kothala himbutu tea), or drinking water that has been stored overnight in mugs made from the plant's roots and stems (23, 24).

Fig 7: Mugs made from the roots and stem parts of *S. reticulata* (23)

Apart from its anti-diabetic potential, the plant is widely used to treat other diseases and conditions. The root decoction is used to treat asthma, amenorrhea, itching, thirst, and swellings (25). The roots and stems of this herbal plant were used for thousands of years for the treatment of rheumatism, gonorrhoea, skin diseases, obesity, and haemorrhoids (17, 23, 26). It is also consumed as a food supplement for the prevention of obesity and diabetes in many countries including Japan and the USA (23). Traditional practitioners have been observed to have developed a system whereby they identify the plants' most useful components for various healthcare applications and continue to use them without the support of conventional clinical trials (15).

3. PHYTOCHEMISTRY

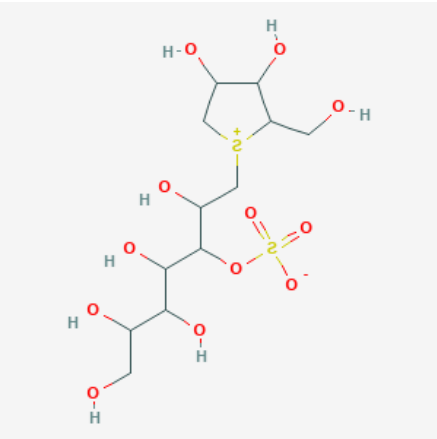
The composition of the numerous chemical components isolated from *Salacia* species varies according to the species, the plant parts under study, and the plants' geographic origins (27). A study (28) compared the levels of salacinol and kotalanol in the roots, stems, leaves, and fruits of *S. reticulata*, *S. oblonga*, and *S. chinensis*, for instance. In comparison to other plant sections and the other two species, the roots of *S. reticulata* contained most of these compounds. Neokotalanol was determined to be the predominant component in samples from Thailand, while salacinol was discovered to be the predominant component in samples from Sri Lanka and India (27).

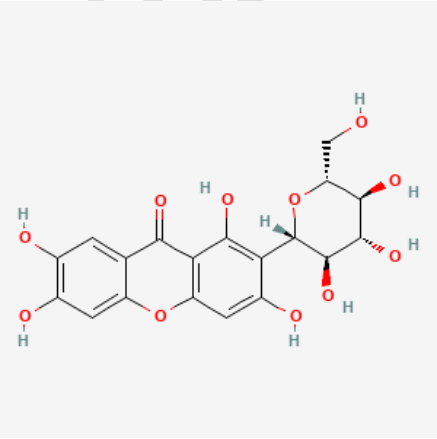
According to Akaki et al. (2014), kotalanol, ponkoranol, salacinol, salaprinol, and sugar-based sufonium sulfates are thought to play a significant role in the anti-diabetic effects of *Salacia* species (27). *S. reticulata* and other *Salacia* species also contain the xanthone mangiferin, which has been proven to inhibit the activities of the enzymes sucrase, isomaltase (glucosidases), and aldose

reductase (30). Mangiferin has been the subject of more pharmacological and mechanistic research than any other Salacia component.
S. reticulata leaves have been used to isolate a number of polyphenolic proanthocyanidin oligomers (31). Epiafzelechin, epicatechin, and epigallocatechin were found to be the main components.These polyphenols were found to inhibit pancreatic lipase activity in hydroalcoholic leaf extracts, demonstrating their ability to lower lipid levels.

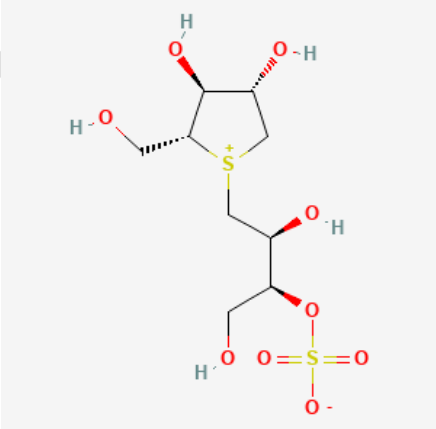
In addition, many minor constituents, such as different triterpenes and sesquiterpenes, have been isolated in *S. reticulata* and other *Salacia* species (15, 32,33, 34). Regarding the pharmacological properties of extracts that have been observed, it is unknown what functions these minor constituents play. Due to the amounts present in the extract, they also don't seem to have noticeable toxicological properties, according to a number of safety studies.

In conclusion, kotalanol, ponkoranol, mangiferin, salacinol, and salaprinol seem to be primarily responsible for Salacia's anti-diabetic effects. The flavanols, Epiafzelechin, epicatechin, and epigallocatechin exhibit to be mainly responsible for the decreasing effects of lipids in Salacia extracts. Salacia contains a number of minor sesquiterpenes and triterpenes, but they may not be found in enough quantities to have an evident pharmacological effect.





Structure of Salacinol (35)Structure of Mangiferin (36)



Structure of Kotalanol (37)

4. PHARMACOLOGY

4.1 Experimental evidence of anti-diabetic and anti-hyperlipidaemic properties of *S. reticulata*

The effectiveness of aqueous *S. reticulata* extracts in controlling the metabolization of carbohydrates has been assessed in a number of human clinical studies. Shimoda et al.'s (1998) one of the first clinical investigations on the hypoglycaemic properties of an aqueous extract of *S. reticulata* demonstrated the extract's potency in lowering postprandial hyperglycaemia (38). Kajimoto et al. (2000) discovered that *S. reticulata* extracts significantly lowered blood glucose levels in comparison to the control group in a double-blind, placebo-controlled study with borderline type 2 diabetics (39).

Using a patented *S. reticulata* formula, Jayawardena et al. carried out a double-blind, single-center, randomized placebo-controlled cross-over study in 2005. For this study, 51 type 2 diabetic patients between the ages of 40 and 65 were chosen. Utilizing HbA1c, fructosamine, and a blood glucose test of six points, the effectiveness of the treatment was evaluated. For three months, the treatment groups drank tea infused with the patented *S. reticulata* preparation. According to the results, the treatment group's HbA1c decreased by 0.54 + SD 0.93, while the placebo group's HbA1c decreased by 0.3 + SD 1.05 ($P < 0.001$). There were no significant negative effects reported, and the tea had no impact on the function of the liver or kidneys. It is unclear how much of the product the subjects actually ingested (24).

In a study published in 2005, Tanimura et al. investigated the effects of a mixture of *S. reticulata* aqueous extract and cyclodextrin on serum glucose and insulin levels upon exposure to a sucrose tolerance test, as well as serum glucose levels over time, in human volunteers. According to the study, people who consumed the aqueous extract prior to consuming sugar had significantly lower postprandial hyperglycaemic levels (40).

In a double-blind placebo-controlled, randomized trial, Shivaprasad et alinvestigated the effect of *S. reticulata* on blood lipids and glycaemic control in 29 individuals with pre-diabetes and mild to moderate hyperlipidaemia. The three groups of patients—placebo, leaf, or root extract—were chosen at random. *S. reticulata* was administered to the treatment groups six weeks in a row at a dose of 500 mg/day. The Oral Glucose Tolerance Test (OGTT) and fasting blood glucose (FBS) were used in assessing the effectiveness of the treatment. After 3 and 6 weeks of treatment, FBS significantly decreased in patients who were randomly assigned with Salacia root extract ($P < 0.01$). The individuals who received the leaf extract did not exhibit a significant decline in FBS until 6 weeks had passed ($P < 0.05$) (41).

30 individuals with type 2 diabetes were given the bark powder of *S. reticulata* (2g in capsule form) for 90 days in Radha and Amrithaveni, 2009. HBA1c, fasting blood glucose, and lipid levels all dropped significantly according to the study (42).

Sim et al., 2010 used X-ray crystallography to investigate the inhibitory effects of the isolated *S. reticulata* constituents de-o-sulfonated kotalanol, kotalanol, and salacinol on human maltase-glucoamylase in the intestine. The de-o-sulfonated kotalanol was found to be the most effective antagonist of this specific enzyme so far, being about ×2000 more effective than common clinically used medications (43).

The excessive production of Advanced Glycation End-Products (AGEs) by non-enzymatic glycation causes a variety of health issues in humans, and the condition of hyperglycaemia significantly speeds up AGE formation. A study was carried out (*in vitro*) in Sri Lanka using 4 plant species including the stems of *S. reticulata* to evaluate the plant’s potential to inhibit the rapid formation of AGEs, reverse glycation, and antioxidant properties. According to the study, the decoction of the plants including *S. reticulata* showed significant anti-AGE forming potency along with the reversal of glycation and antioxidant properties with regard to total flavonoid content, total polyphenol content, ferric iron-reducing power, and DPPH and ABST radical scavenging activities (44).

4.2 Experimental evidence of anti-obesity effects of *S. reticulata*

S. reticulata roots (rich in alpha-glucosidase) are widely used in Ayurveda to treat metabolic disorders, while some are treated with vitamin D3. A study was conducted aiming to ascertain how both *S. reticulata* and Vit D3 would affect obese people. In this study (open-labelled, randomized) they looked at healthy individuals (40) between the ages of 30 to 60 who were physically active and had a body mass index (BMI) between 25 and 45. The participants were divided into two groups (A

and B) at random. Measurements were made of BMI, body weight, and composition. For four weeks, both groups received instructions on how to live a healthy lifestyle and exercise. In addition, group B was advised to take 1 capsule with 200mg of *S. reticulata* along with 1.6g (64IU) of Vit D3 three times per day with their meals. Within 4 weeks, a significant loss of weight and body fat was seen. BMI reduction was achieved because group A lost 1.8 kg or 2.1% of their body weight and group B lost 5.3 kg or 6.1% (p=0.03). These encouraging findings imply that the combination of *Salacia reticulata* and Vitamin D3 may be extremely beneficial and effective in treating overweight and obesity, especially when used in conjunction with a program to change one's lifestyle (45).

4.3Experimental evidence of antioxidant effects of *S. reticulata*

Chandrashekar et al. (2009) investigated the capacity of different *S. reticulata* extracts to scavenge free radicals. Extracts of the bark and root were created using diethyl ether, ethanol, ethyl acetate, petroleum ether, and water. All extracts can scavenge superoxide and hydrogen peroxide, according to *in vitro* studies, but diethyl acetate and petroleum ether extracts are most effective at doing so. (There was no mention of the active ingredients) (46).

In streptozotocin-induced diabetes, hydroperoxides, malondialdehyde, and glutathione levels (tissue markers of oxidative stress) were all significantly decreased after receiving 40 mg of mangiferin per kilogram for 30 days (47).

A root extract of *S. reticulata* was found to have a dose-related inhibition of antioxidant activity and melanin synthesis in UV-irradiated or MSH-induced B16 melanoma cells (48). The authors speculate that the root extract may be useful in treating hyperpigmentation disorders.

4.4Experimental evidence of antimicrobial effects of *S. reticulata*

Choudhary and co-workers used zone of inhibition to test the antimicrobial activity of *S. reticulata* extracts against Escherichia *coli*, *Staphylococcus aureus,Pseudomonas aeruginosa*, *Bacillus subtilis*, and fungal strains including *Candida albicans*, *Candida tropicalis*, *Cryptococcus neoformans*, and *Epidermophyton floccosum*. Both extracts were seen to have inhibitory effects on all of the test microorganisms. However, methanolic extract was less efficient than chloroform extract (49).

Four different extracts of *S. reticulata* (chloroform, ethyl ether, petroleum ether, and methanol) were tested for antibacterial activity against *Escherichia coli*, *Pseudomonas fluorescence*, *Bacillus subtilis*, *Proteus vulgaris*, *Staphylococcus epidermidis*, *Salmonella aboni*, *Pseudomonas aeruginosa*, Salmonella *typhi*, *Shigella sonnei*, and *Vibrio cholerae*. Both zones of inhibition and Minimum Inhibitory Concentration (MIC) were observed. Among the pathogens, *B. subtilis*, *P. vulgaris*, *S. epidermidis*, and *S. sonnei* gave significant inhibitory zones for all extracts. The study proves the significant antibacterial potency of *S. reticulata* (50).

5. ANIMAL-RELATED STUDIES FROM *S. reticulata*

Numerous studies have been conducted with various parts of *S. reticulata in vivo* (with mice). They have proven that this plant has a wide range of pharmaceutical properties including anti-diabetic, anti-hyperlipidaemic, anti-obesity, antioxidant, anti-inflammatory, and many more. Following are a few examples of *in vivo* studies done with *S. reticulata*.

5.1. Hypoglycaemic effect

The aqueous extract of *S. reticulata* root bark has proven hypoglycaemic activity in healthy mice models. In a study, different compounds of the stem and roots of *S. reticulata* were fractionated with respect to polarity. The most active fraction was decided after evaluating each fraction. According to the study findings, a significant effect was shown by the precipitate of methanol fraction, and therefore it was further used *in vivo* on diabetic rats (induced by alloxan) for long-term oral administration. It was administered 2 times per day for 120 days. The study shows that the treatment improved tolerance to glucose while markedly reducing Fasting blood sugar (FBS), glycated Haemoglobin, and fructosamine levels. On the other hand, hyperphagia, polydipsia, and weight loss of rats were also

declined due to the treatment. The findings imply that *S. reticulata* may have an extra-pancreatic effect on the production or clearance of glucose in alloxan-induced diabetic rat models (51).

Im et al., 2009 conducted a study to determine the mechanism(s) by which the aqueous extract of *S. reticulata* reduces FBS levels. This was done in order to track the expression of the genes for the liver's gluconeogenic enzymes both *in vitro* and *in vivo* (in mice). According to *in vivo* RT-PCR and DNA microarray results, the aqueous extract of *S. reticulata* regulates the mRNA levels of genes involved in glucose metabolism in the liver while controlling the expression of a number of genes engaged in the TCA cycle and glycolysis (52).

The aqueous extract of *S. reticulata* leaves was used in a study to observe the absorption of sugars in type 1 diabetic and normal mice. The postprandial increase of plasma glucose and insulin levels along with alpha-glucosidase activity in the intestine was inhibited by a repetitive oral treatment of the extract (1.0 mg/mouse). Giving 0.01% of the plant extract as a substitute for drinking water stopped the rise of plasma glucose levels and alpha-glucosidase activity in type 1 diabetic mice. This specific treatment has also prevented the increase of plasma, kidney, and pancreatic levels of lipid peroxides, the increase of aldose reductase activity in the kidney, and the decrease of plasma insulin levels. Therefore, the study proves that the aqueous extract of S*. reticulata* leaves can be effective in the prevention of obesityand diabetes due to its many effects (53).

5.2 Anti-hyperlipidaemic and anti-obesity effects

Research was carried out in Japan (2006) using *S. reticulata* aqueous extract and cyclodextrin to observe their effects on the increase of plasma triglyceride (TG) levels that were stimulated by oral treatment of a liquid diet rich with fats to Sprague-Dawley male rats. There was a significant decrease in the TG levels among the treated rats compared to the controlled group, 4 hours after the administration of the HF diet. The researchers also studied female C57BL/6 mice that were given a solid high-fat diet ranging from 0, 0.2, or 0.5% of treatment for 8 weeks. The elevation of visceral fat mass and body weight were observed as comparatively low among the mice who were given 0.5% of treatment than other groups. Finally, the study concluded that the reduction of carbohydrate and lipid uptake from the small intestine may be responsible for the inhibitory effects of the treatment on high-fat diet-induced obesity. Consequently, the extract of *S. reticulata* along with cyclodextrin may prevent the visceral fat storage and intolerance to glucose that develops this particular type of obesity (54).

A study was carried out to elucidate the mechanisms of *S. reticulation* obesity and safety both *in vivo* and *in vitro*. For 2 months, the investigators fed Tsumura Suzaki Obesity Diabetes (TSOD) mice (a spontaneous obese mice model with type 2 diabetes) and Tsumura Suzaki non-obese (TSNO) mice (the corresponding control group) a regular MF diet, either alone or combined with *S. reticulata* (0.3 or 1.0%). In comparison to the control group, TSOD mice developed multiple signs and symptoms of metabolic diseases and grew to be obese as a result of the accumulation of fat. On the other hand, the TSOD group exhibited effects including, suppression of fat accumulation and increase of body weight, reduction of abnormal glucose tolerance and lipid metabolism along with intrahepatic suppression of fat accumulation. The adipose hypertrophy in the mesentery, which was observed in TSOD mice was also prevented by *S. reticulata* (55).

5.3. Hepatoprotective and antioxidant effects

Using a liver injury model induced by oxidative stress, the liver protective properties of methanol and hot water extracts of *S. reticulata* roots and stems were investigated. Here, a mouse model treated with Carbon tetrachloride (CCl_4) was used as the study group. They were treated with the extracts (400 mg/kg) which markedly decreased the rise in liver markersALT and AST. Additionally, these extracts resulted in the reduction of TBA-RS production, a marker of elevated hepatic lipid peroxidation caused by exposure to CCl_4. The findings imply that the hepatoprotective properties of *S. reticulata* are related to the antioxidant activity of the main phenolic compounds (56).

5.4. Anti-inflammatory effects

A study looked into the ability of the *S. reticulata* leaf to treat the collagen antibody-induced arthritis (CAIA) model of rheumatoid arthritis (RA) in mice, both *in vivo* and *in vitro*. The mice were given either

a 1% (w/w) *S. reticulata* powder diet or a chow diet (AIN-93G). Every mouse was bred for 23 days. Mice were put to death 7 or 14 days after receiving an injection of LPS, and blood and tissue samples were taken.mRNA levels of genes associated with inflammation and osteoclasts, Serum levels of inflammatory mediators, andhistological analysis were all conducted. In comparison to CAIA mice, the treatment reduced the inflammatory cell infiltration, the rapid initial paw swelling, damage to the skeletal system, the mRNA levels for genes associated with osteoclasts, and osteoclast activation. Inflammatory mediators' mRNA levels and serum, however, were the same in mice treated with CAIA and *S. reticulata* extract. By regulating osteoclast genesis, *S. reticulata* extract may be able to lessen the induction of inflammatory cells and the degradation of skeletal tissue by CAIA (57).

6. SAFETY EVALUATION

As already mentioned, herbal remedies made from *S. reticulata* and other *Salacia* species have been used for many years in traditional folk medicine to treat a variety of illnesses without any reported side effects (24, 40, 41). Following are some studies that prove the safety of using S. *reticulata* for medicinal purposes.

The antigenicity and phototoxicity of the water-soluble extract from *S. reticulata* were examined in a study on guinea pigs. In the active systemic anaphylaxis reaction, neither the oral administration group nor the subcutaneous administration group displayed any anaphylactic reaction. In the phototoxicity study, consumption of *S. reticulata* extract did not result in erythema or oedema. These results show that the extract of *S. reticulata* is neither phototoxic nor antigenic (58).

A study used a gene expression DNA microarray to assess the safety of an aqueous extract of *S. reticulata* stem in mice. For three weeks, the extract was given every day. The assay evaluated the expression of genes involved in cell function, inflammatory/immune response, metabolism, ribosomal proteins, and stress response. Based on the absence of an impact on these parameters, the authors came to the conclusion that the extract was non-toxic (59).

According to an assessment of its safety *in vivo*, Salacia extract (both *S. reticulata* and *S. oblonga*) in doses ten times greater than those recommended for humans for 14 days did not significantly affect the weight of organs, blood chemistry, and haematology (60)

Furthermore, implantation index, uterine implants, and gestation index were unaffected by oral administration of the *S. reticulata* root extract during early or mid-pregnancy. However, women whose pregnancies are complicated by diabetes should avoid using the *S. reticulata* extract because it may pose a significant risk to a healthy pregnancy (61).

Clinical trials are necessary to further support the safety of the use of Salacia extracts, even though numerous rodent toxicological studies have shown that *S. reticulata* has little to no adverse effects. According to research, the management of diabetes and obesity with this specific traditional medicine meets a multiple-target strategy. Additional experimental investigations are needed to show how different *S. reticulata* applications interact with other therapeutic interventions (15).

7.MECHANISM (S) OF ACTION AND ROLE OF PHYTOCHEMICALS BEHIND ANTI-DIABETIC, ANTI-OBESITY, AND ANTI-HYPERLIPIDAEMIC EFFECTS OF *S. reticulata*.

Phytochemicals are compounds that are produced naturally by plants as a form of secondary metabolites. Many of them come with therapeutic properties (62). *Salacia reticulata* has been found to be rich in kotalanol, mangiferin, and salacinol, which are responsible for the extensive medicinal potency of this plant. Mangiferin, known as 1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside, is a bioactive compound primarily derived from the mango tree. It exhibits strong antioxidant properties and a wide range of pharmacological effects, including analgesic, antibacterial, antidiabetic, anti-hyperuricemia, anti-inflammatory, antipyretic, antitumor, antiviral, cardioprotective, immunomodulatory effects, neuroprotective, and regulation of lipid metabolism. Due to these diverse health-promoting attributes, mangiferin shows promise for further research and development. Nevertheless, its low solubility, limited mucosal permeability, and constrained bioavailability pose challenges to its clinical therapeutic use, necessitating chemical and physical modifications to broaden its application (63).

Kotalanol is a natural α-glucosidase inhibitor present in S. reticulata and identified by guided bioassays. Through chemical and physicochemical analyses, the structure of kotalanol was determined to be an inner salt consisting of a 1-deoxyheptosyl-3-sulfate anion and a 1-deoxy-4-thio-D-arabinofuranosyl sulfonium cation. Notably, kotalanol exhibited stronger inhibitory activity against sucrase compared to salacinol and acarbose, showcasing its potential as an effective α-glucosidase inhibitor (64). Furthermore, the active sulfonium constituents kotalanol, neokotalanol, and salacinol were evaluated for their α-glucosidase inhibitory activity using human α-glucosidases. It was found that these compounds exhibited potent inhibition of human α-glucosidases, with IC_{50} values ranging from 3.9 to 4.9 μM for maltase, similar to their inhibitory effects on rat small intestinal α-glucosidase. These principal sulfonium constituents demonstrated high stability in artificial gastric juice and showed minimal absorption from the intestine in experiments using *in vivo* models (in-situ rat-ligated intestinal loop model). These findings suggest that these sulfonium compounds hold promise as potential candidates for novel anti-diabetic agents. Thus, the α-glucosidase inhibitory activity, which was established as the mechanism of action for the antidiabetic effect of *S. reticulata* through *in vitro* investigations, was further confirmed *in vivo* studies (65).

Researchers identified the primary mechanism responsible for *S. reticulata*'s hypoglycaemic effect as alpha-glucosidase inhibition (through bioassay-guided isolation of the active fraction) (66). Within the small intestine, alpha-glucosidase and alpha-amylase work together to convert dextrin, maltose, starches, and sucrose into easily absorbable monosaccharides. The inhibition of these enzymes causes a delay in glucose absorption, which can help reduce the postprandial glucose spikes seen in diabetics. This mechanism is currently used in clinical treatments that involve alpha-glucosidase inhibitors like Acarbose (67). As a result, it is reasonable to expect that extracts derived from *S. reticulata* would effectively reduce postprandial hyperglycaemia and hyperinsulinemia by inhibiting poly and oligosaccharide digestion. According to studies, maltose and sucrose challenges on rats show that methanolic and/or 80% aqueous methanolic extracts from *S. reticulata* have inhibitory effects on glucose levels. Rats fed only glucose did not experience this inhibitory effect, indicating that *S. reticulata* has a unique effect on brush border enzymes (66).

Furthermore, Researchers have looked closely at *Salacia* species to see if it can help with weight loss. One important enzyme in the body helps digest the fat we eat, and it's called pancreatic lipase. Slowing down this enzyme is thought to be helpful for reducing weight. The hot water extracts from *S. reticulata* also reduce the activity of pancreatic lipase. So, the main way Salacia root helps lower high levels of fat in the blood after eating is by slowing down this enzyme in the small intestine (16, 68).

For a long time, adipocytes were thought to be primarily a tissue dedicated to storing excess energy. Recent evidence suggests they play an endocrine role in regulating glucose and lipid metabolism by actively releasing different kinds of adipocytokines (69). Adipocytes are classified into three stages: premature, mature, and hypertrophic, with each stage producing different adipocytokines. Adipocyte hypertrophy has been linked to the development of a number of metabolic diseases, including cerebrovascular diseases, insulin resistance, ischemia that can develop into cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD) (70). Therefore, the modulation of these adipocytes may indeed influence fat accumulation and its subsequent impact on cardiac and cerebrovascular diseases (71). A study by Shimada et al. in 2011 investigated the differentiation of mouse-derived adipocyte precursors in the presence of *S. reticulata* extracts. The study found that these extracts significantly inhibited the differentiation of precursor cells into mature adipocytes. Additionally, there was an inhibitory effect on the expression of Peroxisome Proliferator-Activated Receptor-gamma (PPAR) and a reduction in the concentration of adiponectin. Previous research has suggested that *S. reticulata* might directly act on adipocytes to prevent obesity (PPAR-gamma is thought to promote the transformation of pre-adipocytes into mature cells, and adiponectin, released from adipocytes, improves insulin resistance and arteriosclerosis). However, the impact of Salacia administration on adiponectin levels remains a subject of controversy (70, 71).

CONCLUSION

Since ancient times, *Salacia reticulata* has been used to treat diabetes and obesity. Today, research using this valuable plant has shown that it has a variety of medicinal effects, including anti-

inflammatory, antibacterial, anti-hyperlipidaemic, antioxidant, and many more. It has been discovered to be abundant in essential phytochemicals and secondary metabolites, which aid in the display of a variety of therapeutic effects. therefore. *S. reticulata* can be referred to as a promising herbal plant that can treat a variety of human illnesses and disorders as no significant adverse effects were reported from the toxicological studies conducted on this plant. However, In the future, it will be necessary to conduct carefully planned studies on both human and animal subjects, specifically addressing the long-term effects and safety of *S. reticulata* treatment, as well as studies involving a larger number of human subjects.

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