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Phyto-constituents, Pharmacological Properties and Biotechnological Approaches for Conservation of the Anti-diabetic Functional Food Medicinal Plant Salacia: A Review Note

Majid Bagnazari[*1], Mehdi Saidi[1], Madhusudhan Mudalabeedu Chandregowda[2], Harishchandra Sripathy Prakash[2], Geetha Nagaraja[2]*

1- Department of Horticulture Sciences, College of Agriculture, University of Ilam, Ilam-69315-516, Iran

2- Department of Studies in Biotechnology, Manasagangotri, University of Mysore, Mysuru-570006, Karnataka, India

Abstract

Background and Objective: Genus *Salacia L.* (*Celastraceae*) is a woody climbing medicinal plant consisting of about 200 species with many endangered species located throughout the world's tropical areas. Various parts of the plant as food, functional food additive and tea have been extensively used to treat a variety of ailments like diabetes and obesity as well as inflammatory and skin diseases. The present work reviews the phytochemical properties, pharmacological activities, biotechnological strategy for conservation and safety evaluation of this valuable genus.

Results and Conclusion: More efforts are needed to isolate new phytoconstituents from this important medicinal plant. The mechanism of anti-diabetic action has not been done at molecular and cellular levels, thus the fundamental biological understanding is required for future applications. Though the safety of plant species has been well documented and has been confirmed by many toxicological studies, further toxicity research and clinical trials are recommended. In order to sustain harvest and conservation, agronomic practices for cultivation have to be developed. Establishment of more efficient protocols for in vitro propagation is necessary too. Approaches like genetic manipulation, hairy root culture, media standardization, and use of inducers/precursors for elevation of secondary metabolite levels could also be attractive.

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*Corresponding author:
Majid Bagnazari
Department of Horticulture Sciences, College of Agriculture, University of Ilam, Ilam, P.O.Box: 69315-516, Iran.

Tel: +98-843- 2227015
Fax: +98-843- 2227015
E-mail:
majid.bagnazari@gmail.com

1. Introduction

Genus *Salacia L.* (*Celastraceae)* consists of about 200 species. The plants are lianes, shrubs or small trees, rarely shrublets, and widely distributed in India, Sri Lanka and China. This genus can be found in the Southeast Asian countries such as Thailand and Indonesia, and in torrid zones like Brazil [1]. Within India, it is distributed in semi-evergreen Western Ghat forests of Karnataka, Kerala (Coastal forests of Kollam, Western Ghats of Pathanamthitta and Idukki districts) and Southern Orissa [2]. It is represented by 21 species in this country; among them, 15 species are known to occur in Peninsular India out of which, *S. reticulata* and *S. oblonga* are predominant species [3].

The roots, rootbarks, stems, dried parts and water extracts of the whole plant have been extensively used in the Ayurvedic system of Indian traditional medicine and in some Southwest Asian countries to treat a variety of ailments. Numerous biologically active compounds, such as anthocyanidins, triterpenes, phenolic compounds, glycosides and coloring agents have been isolated from the plants of the *Salacia* species, which show various medicinal properties [4]. The plant and its extracts have been evaluated for number of activities like anti-diabetic, anti-hyperlipidemic, anti-inflammatory, tonic, blood purifier and (as a preventive food) for lifestyle-related diseases [5,6].

Table 1. The major phytochemicals isolated from different species of the genus *Salacia*

Species	Phytochemical/s	Plant part(s)	Ref.
S. prinoides	Salaprinol; ponkoranol; salacinol and kotalanol	Root and stem	[10]
S. madagasca-riensis	Isoiguesterin	Root	[11]
S. oblonga	Kotalagenin 16-acetate	Root	[12]
S. reticulata	Kotalanol	Root and stem	[13]
S. reticulata	Mangiferin	Root bark	[14]
S. reticulata	(-)-Epicatechin; (-)-epigallocatechin; (-)-4'-O-methylepigallocatechin; (-)-epiafzelechin-(4ß 8)-(-)-4'-O-methylepigallocatechin; (-)-epicathechin-(4ß 8)-(-)-4'-O-methylepigallocatechin	Root	[15]
S. reticulata	Salacinol	Root and stem	[16]
S. chinensis	Phenolic glycosides, foliachinenosides A1, A2, A3, B1, B2, C, and D	Leaf	[17]
S. chinensis	Four dammarane-type, three lupane-type, and an oleanane-type triterpenes named foliasalacins A1, A2, A3, A4, B1, B2, B3, and C	Leaf	[18]
S. chinensis	Megastigmane glycosides foliasalaciosides A1, A2 , B1, B2, C, and D	Stem and Leaf	[19]
S. chinensis	Proanthocyanidins: Pentaacetate; Trimethyl ether; Hexamethylether; Octaacetate; Heptadecaacetate; Dodecamethylether	Root and stem	[20]
S. chinensis	1,3-diketofriedelane derivatives: six closely-related triterpenes, P, Q, R, S, T and V	Root bark	[21]
S. prinoides	Salacia Diketone-A	Root bark	[22]
S. prinoides	1,3-diketone A; 1,3-diketone B	Root bark	[23]
S. prinoides	25, 26-oxido-friedel-1, 3-dione	Root bark	[24]
S. chinensis	Triterpens: 28-hydroxy-3-oxo-30-lupanoic acid; 3-oxo-lupane-30-al; 29-nor-21α-H-hopane-3,22-dione; 21α-H-hop-22(29)-ene-3β , 30-diol; and betulin	Stem	[16]
S. chinensis	Salasones A; salasones B; salasones C; Salaquinone A; salasol A	Stem	[25]
S. chinensis	Salasones D; salasones E; salaquinone B; salasol B	Stem	[26]
S. chinensis	Three D:B-friedobaccharane skeleton triterpenes named foliasalacins D1; foliasalacins D2; and foliasalacins D3	Leaf	[27]
S. reticulata	Kotalagenin 16 acetate; 26-hydroxy1,3 fridelanedione; maytenfolic acid; 3β,22 β dihydroxy olean-12en- 29 oic acid	Root bark	[28]
S. reticulata	2lα, 26-dihydroxy-D; iguesterin; pristimerin.	Stem bark	[29]
S. beddomei	Salacianone and salacianol	Stem bark	[30]
S. beddomei	20, 29-Epoxysalacianone; 6β-hydroxysalacianone	Stem bark	[31]
S. prenoides	Friedel-1-0ne-3-one; Friedelane-1,3-dione-7α-ol; Friedelane-1,3-dione-24-al	Root bark	[32]
S. verrucosa	21α-hydroxyfriedelane-1,3-dione; 30-hydroxyfriedelane-1,3-dione; friedelane-1,3-dione; 26-hydroxyfriedelane-1,3-dione; friedelin; 21α-hydroxy-D:A-friedo-olean-3-one; and kokoonol	Stem	[33]
S. reticulata	Isoiguesterino; 30-hydroxypristimerin	Root bark	[34]
S. leptoclada	Pentacyclic triterpenic quinone methide	Stem bark	[35]
S. amplifolia	Friedelin; 2-hydroxyfriedelan-3-one; D-friedoolean-14-en-3-one; 3-(300, 400-dihydroxy-transcinnamoyloxy)-D; friedoolean-14-en-28-oic acid; lupeol; lup-20 (29)-en-3, 21-dione; 3, 22-dioxo-29-normoretane.	—	[36]
S. hainanensis	(2β,3β-dihydroxylup-20(29)-ene; 30-hydroxy-D:A-friedo-olean-1-en-3-one; 24,25,26-trihydroxytirucall-7-en-3-one; olibanumol J; 21α-hydroxy-D:A-friedo-olean-3-one and 29-hydroxy-D:A-friedo-olean-3-one.	Root	[37]
S. cordata	28-hydroxylup20(29)en-3-one; 30-hydroxylup20(29)-en-3-one; botulin; pyracrenic acid; 15,28-dihydroxylup20(29)-en-3-one	Stem bark	[38]
S. reticulata	Salaciquinone; isoiguesterin	Root bark	[39]
S. hainanensis	Thirteen triterpenoids (1-13), including two new lupane triterpenoids, salacinins A and B (1 and 2), as well as one new friedelane triterpenoid, salacinin C (3)	Roots and stem	[40]

Table 1. (Continued)

Species	Phytochemical/s	Plant part/s	Ref.
S. longioes	Salaterpene A; salaterpene B; salaterpene C; salaterpene D; 1α,6β-diacetoxy-8β,9β-dibenzoyloxy-4bhydroxy- 2-oxo-dihydro-β-agarofuran; 2 β -acetoxy-1α,6β,9 β -tribenzoyloxy-4 β -hydroxy-dihydro-bagarofuran.	Seed	[41]
S. beddomei	1β,15α-dihydroxy-friedelan-3-one	Stem bark	[42]
S. lehmbachii	Lehmbachols A, B, C and D.	Bark	[43]
S. campestris	22β-hydroxymaytenin; 20α-hydroxymaytenin; celastrol and netzahualcoyone	Root bark	[44]
S. macrophylla	Pristimerin; netzahualocoyene; netzahualocoyonol; 2,3,7-trihydroxy-6-oxo-1,3,5(10),7-tetraene-24-nor-friedelane-29-oic acid methyl ester	Root	[45]
S. chinensis	Neoponkoranol and neosalaprinol	Stem	[9]
S. campestris	Salacin; pristimerin; maytenin; 20alpha-hydroxymaytenin; netzahualcoyene	Root bark	[46]
S. verrucosa	30-hydroxyfriedelane-1,3-dione; 21α-hydroxyfriedelane-1,3-dione	Stem	[47]
S. reticulata	Quinonemethide; 15 α hydroxy friedeelan 3 one; Lehmbachol C; Lehmbachol D; Pristimerin; Lehmbachol A.	Root	[48]

There is a narrow border between drugs and foods; hence, production of functional foods has recently placed an important rank on the international markets. These days, various parts of *Salacia* most commonly used as food, functional food additive and tea (3g×25 tea bag) sell by many branded names such as Salsulin, Vitacost and Vee nurse throughout the world even in Amazon for treating diabetes and obesity. *S. oblonga* has been extensively used as a food ingredient in countrie such as Korea, Japan, Sri Lanka and India for high glucose level adjustment [7].

This paper reviewed previous studies on phytochemical and pharmacological properties that have been conducted so far on this medicinally important genus. Biotechnological strategies for conservation and safety evaluation of the plant parts/extracts are the main parts of the present review.

2. Phytochemical properties

Anthocyanidins as common antioxidant plant pigments and coloring agent of beverages and fruit juices, catechins natural antioxidants rich in green tea and dulcitol a sugar alcohol (that is reducted product of galactose) have been isolated from the plants of *Salacia* species. Phenolic acids, quinones, triterpenoids and mangiferin (a known antimicrobial and antioxidant biocompound) are the other studied biochemicals of this plant genus. Several most potent natural α-glucosidase inhibitor phytochemicals (named salacinol, neosalacinol, kotalanol, neokotalanol, ponkoranol, neoponkoranol, neosalaprinol and salaprinol) have also been extracted from *Salacia* species responsible for postprandial anti-hyperglycaemic activities [8,9].

3. Pharmacological activity

Anti-diabetic (especially type 2 diabetes), anti-inflammatory, nephroprotective, anti-oxidant and anti-tumor activities are the main pharmacological properties of the genus *Salacia* [49]. The root bark (either boiled in oil or decoction or powder) is used in the treatment of rheumatism, gonorrhoea, itches and asthma, thirst, ear diseases, hepatitis, cardiac disorders, arthritis, insulin resistance, carminative, emmenagogue, blood tonic, and cardiotonic purposes, leucorrhea and stimulated lochial excretion [50]. The multi-target regulatory activities of root such as peroxisome proliferator-activated receptor-alpha-mediated lipogenic gene transcription, angiotensin II/angiotensin II type 1 receptor, alpha-glucosidase, aldose reductase and pancreatic lipase are at least in part due to the presence of mangiferin, salacinol, kotalanol and kotalagenin 16-acetate. These multi-target actions may mainly contribute to the improvement of type 2 diabetes and obesity-associated hyperglycemia, dyslipidemia and related cardiovascular complications seen in humans and rodents [51].

3.1 Anti-diabetic activity

The maximum reduction in fasting blood glucose level (30%) was observed 3 hours after administration of S. reticulata aqueous decoction in Sprague-Dawley rats [52]. Aqueous extracts of *S. reticulate* (100 g of plant stem contained 241.8 mg 13-MRT (13-membered ring thio-cyclitol) and 252.5 mg salacinol) showed the significant lowering of postprandial glucose levels on maltose- and sucrose-loaded male Wistar rats [53]. Potent anti-hyperglycemic effects of methanolic extract from the stems of *S.chinensis* in oral sucrose or maltose-loaded fed rats have been confirmed based on inhibitory effects on intestinal alpha-glucosidase, rat lens' aldose reductase, formation of amadori compounds and advanced glycation end-products, nitric oxide production from lipo-polysaccharide activated mouse peritoneal macrophage, and radical scavenging activities [54].

Table 2. Pharmacological activities of *Salacia* species

Species	Activity	Model	Used part/s	Conclusion	Ref.
S. chinensis	Anticancer	Four cancer cell lines Hep-G2, LU, KB, and MCF-7.	8 isolated triterpenoids	Significant activity against all four tested cell lines by 7α, 21α-dihydroxyfriedelane-3-one triterpenoid	[58]
S. chinensis	Anti-diabetic	Maltose or sucrose loaded rats	Methanolic extract of stems	Inhibitory effects on intestinal α-glucosidase	[59]
S. chinensis	Antihyperlipidemic	Triton-induced and atherogenic diet-induced hyperlipidemic rat	Root extract	Significant antihyperlipidemic activity by chloroform and alcoholic extract of roots	[60]
S. chinensis	Antimicrobial	By disc diffusion and broth dilution methods against pathogens	Crude ethanolic and aqueous extracts	Ethanolic extract possesses significant antifungal than antibacterial activities.	[61]
S. chinensis	Anti-mutagenic	Mutagenicity induced by mutagen in *S. typhimurium* TA98 and TA100	Ethanol extract of mangiferin	Highly effective against reducing the mutagenicity	[62]
S. chinensis	Hepatoprotective	Wistar strain of albino rats	Ethanolic extract of dried bark	CCl4-induced hepatic injury was inhibited significantly	[63]
S. chinensis	Hypoglycemic	Randomized, double-blind, placebo-controlled, in healthy volunteers.	(1000 mg extract of S. chinensis)	Lowering the post-prandial plasma glucose levels	[64]
S. chinensis	Immuno-modulatory	Swiss albino rats	Aqueous extract	Humoral and cellular immune response clearly boosted	[65]
S. chinensis	Reproductive outcome	Sprague–Dawley rats	Plant extract	Had no effect on the reproductive outcome	[66]
S. oblonga	Anti-diabetic	Sucrose- and maltose-loaded rats	Aqueous methanolic extract	Inhibitory activities on α-glucosidase and aldose reductase	[12]
S. reticulata	Anti-diabetic	Inhibitory activities against several carbohydrate metabolize enzymes	Mangiferin, 3 catechins, and 2 catechin dimers isolated from root	Mangiferin was found to inhibit sucrase, isomaltase and aldose reductase.	[15]
S. chinensis	Radical Scavenging	___	Stem	Significant radical scavenging activity	[26]
S.leptoclada	Anticancer	P388 leukemia cells	Acetonic extract of stem bark	Cytotoxic effect with an IC_{50} value of 0.041±0.020 µg per mililitre	[35]
S. longipes	Antimalaria	W2 strain of *P. falciparum*.	Seed extracts	Moderate antiplasmodial activities	[41]
S. chinensis	Anti-obesity and anti-diabetogenic	Oral sucrose or maltose-loaded rats	Stem's methanolic extract	Potent anti-hyperglycemic effects	[54]
S. reticulata	Anti-diabetic and antiobesity	Type 1 diabetic mice	Leaf water extract	Preventing the elevation of diabetes and obesity	[55]
S. oblonga	Hypoglycemic and antioxidant	STZ diabetic rats	Root bark's petroleum ether extract	Significant inhibition of hyperglycemia and hypoinsulinaemia Antioxidant activity in heart tissue	[56]
S. reticulata	Hypoglycemic and hypo-lipidaemic effect	Patients with type 2 diabetes mellitus.	2 g of *S. reticulata* powder daily	Insignificant reduction in fasting blood glucose, HbA1c and lipid levels	[67]
S. reticulata	Antiobesity	Female Zucker fatty rats	Root water extract	Antiobesity effects through inhibition of fat metabolizing enzymes (PL, LPL and GPDH)	[68]
S. oblonga	Acute-glycemic	Patients with type 2 diabetes	Herbal extract	Significant effection	[69]
S. reticulata	Oxygen comsumption and fat accumulation	Normal male C57BL/6J mice	Aqueous extract of stem	Significant reduction in body weight gain, thus lowering fat accumulation and increasing oxygen consumption	[70]
S. reticulata	Hypoglycemic and hypolipidemic effects	STZ juvenile diabetic rats	The combined extract of *S. reticulata* and *C. roseus*	Significant reduction in blood glucose, serum cholesterol and triglycerides	[71]
S. oblonga	Diabetic- induced renal fibrosis inhibition	ZDF rats	Aqueous extract	Attenuates diabetic renal fibrosis. Mangiferin is an effective anti-fibrogenic agent.	[7]
S. reticulata	Hypoglycemic	Alloxan diabetic rats	Powdered root and stem	Hypoglycemic effect through an extrapancreatic effect on glucose production or clearance	[72]
S. reticulata	Adipocyte differentiation	Mouse-derived adipocyte precursor 3T3-L1 cells	Concurrent administration and isolated mangiferin.	Inhibitory action on adipocyte differentiation. Mangiferin caused no suppression of fat accumulation.	[73]
S. oblonga	Anti-mutagenic	Sperm abnormality test in Wistar rats	Extract of root bark	Suppressing the changes induced by Mitomycin-C. Inhibited sperm shape abnormality and number	[74]

Table 2. (Continued)

Species	Activity	Model	Used part/s	Conclusion	Ref.
S. oblonga	Nephroprotective and antioxidant	Acetaminophen (APAP) APAP-induced toxicity in rats	Ethanol extract	APAP significantly increases the levels of serum urea, creatinine, and reduces levels of uric acid concentration. Potent nephroprotective and antioxidant effects	[75]
S. oblonga	Hypolipidemic and biochemical changes	Aluminium toxicity induced white albino wistar female rats	Powder extract	Decreasing total cholesterol, triglyceride and total protein levels Lowering the serum alkaline phosphatase, aspartate aminotransferase, urea, bilirubin and creatinine	[76]
S. oblonga	Antimicrobial	Gram + & Gram – microbial pathogens	Root, stem and leaf powders	Active against eleven microbial pathogens with a broad range	[77]
S. oblonga	Antibacterial	Pathogenic bacteria like *S. epidermidis, E. faecalis*	Stem, leaf and root extracts	Root extract against *Bacillus subtilis* showed higher inhibition than aerial part.	[78]
S. oblonga	Anti-hypertriglyceridemic	Laying hens	Aqueous root extract	Ameliorated hypertriglyceridemia and excessive ectopic fat accumulation	[79]
S. oblonga	Anti-diabetic	KK-Ay/TaJcl type 2 diabetic model mice and human with premetabolic syndrome	Extract of the plant and IP-PA1 (SI tea)	Reduction of plasma glucose levels in mice Reduction of fasting plasma glucose and HbA1c in hyperlipidemia group. Reduction of low and high-density lipoprotein levels in high plasma glucose group	[80]
S. oblonga	Improvement of cardiac lipid metabolism	ZDF rats	Chronic oral administration	Reduction of cardiac triglyceride and FA contents and decrease of the oil red o-stained area in the myocardium	[81]
S. reticulata	Anti-hyperglycemic	Patients with prediabetes	Leaf and root bark extracts	Significant reduction of low-density lipoprotein cholesterol and fasting blood sugar levels	[82]

Inhibition of the plasma glucose and insulin levels' postprandial elevation and intestinal α-glucosidase activities in type 1 diabetic mice was reported as the consequence of water extract administration prepared from the leaves of *S. reticulata* at a dose of 1.0 mg per mouse with maltose or sucrose [55].

Hyperglycemia and hypoinsulinaemia were prevented by administration of *S. oblonga* root bark extract [56]. Consumption of dehydrated *S. chinensis* led to significant reduction in mean blood glucose and cholesterol levels in albino mice and a significant reduction in body weight, serum triglycerides and cholesterol in humans [57].

3.2 Anti-obesity activity

Various species of *Salacia* have been utilized as a supplementary food in countries such as India, US, Japan and other countries to prevent obesity [50]. Anti-obesity effect of *S. reticulata* was confirmed by oral administration of hot water–soluble extract (SRHW). 125 mg per kg body weight for 27 days tended to suppress the body weight and periuterine fat storage through inhibition of fat metabolizing enzymes (PL, LPL, GPDH) and enhanced lipolysis [68]. A potential mechanism for improvement of postprandial hyperlipidemia and hepatic steatosis in diabetes and obesity was observed from both in vivo and in vitro chronic oral administration of *S. oblonga* root water extract to Zucker diabetic fatty rats functioned as a PPAR-alpha activator [83]. Based on the results provided by measurement of body weight, food intake, plasma biochemistry, visceral and subcutaneous fat, glucose tolerance, blood pressure, pain tolerance and histopathological examination, the extracts of *S. reticulata* possess an anti-obesity effect and suppress hyperglycemia in model TSOD (Tsumura, Suzuki, Obese, Diabetes) mice [84].

3.3 Hepatoprotective and antioxidant activity

The hepatoprotective effect of *S. reticulata* extracts (400 mg per kg body weight) using an oxidative stress-induced liver injury model significantly suppressed the increase in glutamic oxaloacetic transaminase and glutamic pyruvic transaminase activities in the carbon tetrachloride (CCl_4)-treated mice [43]. Salacin, a new quinonemethide triterpene isolated from the root bark of *S. campestris*, showed radical scavenging activities towards DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) [46]. Some norfriedelane-type triterpene, lignan and catechin constituents isolated from *S. chinensis* were found to show radical scavenging activity, and their potent anti-oxidant activity was confirmed by nitric oxide production from lipopolysaccharide-activated mouse peritoneal macro-phage and radical scavenging activities [26,54].

3.4 Cardiovascular activity

Oral administration of *S. oblonga* root extract reduces cardiac triglyceride and fatty acid (FA) contents and dec-reases the oil red O-stained area in the myocardium, which parallels the effects on plasma triglyceride and FA levels. These findings suggest the improvement of excess cardiac lipid accumulation and increased cardiac FA oxidation in diabetes and obesity, which occurs by reduc-tion of cardiac FA uptake, thereby modulating cardiac peroxisome pro-liferator-activated receptor alpha-mediated FA metabolic gene transcription [81]. A strong inhibition of α-glucosidase activity in vitro was confirmed by chronic administration of *S. oblonga* extract, which markedly improved interstitial and perivascular fibrosis in the hearts of obese Zucker rat and

reduced plasma glucose levels in non-fasted OZR [85]. A potential cardioprotective role of *S. oblonga* was confirmed by cardiac hypertrophy reduction at least in part through inhibiting cardiac angiotensin II type 1 receptor overexpression [86].

3.5 Anti-inflammatory activity

The anti-inflammatory properties of *S. oblonga* root bark powder and *A. tetracantha* leaf powder able them to suppress the transudative, exudative and proliferative components of chronic inflammation. The increased acid and alkaline phosphatase activity and decreased serum albumin were normalised after treatment with the above mentioned powders. It is suggested that these phyto-chemicals may exert their activity by antiproliferative, antioxidative and lysosomal membrane stabilization [87]. *S. reticulata* treatment ameliorated the rapid initial paw swelling, inflammatory cells infiltration, skeletal tissues damage, osteoclast activation and the mRNA levels for osteoclast-related genes compared with collagen antibody-induced arthritis mice. SRL might reduce the induction of inflammatory cells and degradation of skeletal tissue by collagen antibody-induced arthritis through osteoclasto-genesis regulation [88].

4. Biotechnological strategies for conservation

Plant tissue culture technique (in vitro propagation), as one of the great achievements of biotechnology in recent years, offers many applications, especially in easy regeneration of hardly plant species propagated by traditional systems or production of the healthy and pathogen-free plants. Lack of proper cultivation practices, destruction of plant habitats, excessive and indiscriminate collection for supplementation of global demands, especially obvious anti-diabetic properties have caused most *Salacia* species be categorized as threathened or endangered species [89]. There has been an increased interest in using plant tissue culture in mass propagation and conservation of medicnal plants and various species of *Salacia* plant for recovery of endangered species, thus reducing the risk of extinction [90].

Although most of the *Salacia* plants are severly under threatened or extinction, only a few micropropagation systems were reported in order to regeneration of plant species in previous studies [91-93]. *S. oblonga* has been propagated successfully through in vitro conditions using nodal segments on Murashige and Skoog medium supplemented with various concentrations of plant growth regulators [91].

Efficient propagation protocols for direct organogen-esis of *S. reticulate* (most efficient shoot multiplication on Murashige and Skoog medium fortified with 3.5 mg per litre benzyl adenine and 0.5 mg per litre indole-3-acetic acid) and *S. chinensis* (best shoot regeneration rate on Murashige and Skoog medium supplemented with 1.0 mg per litre 6-Benzylaminopurine and 0.5 mg per litre naphthalene acetic acid) in consideration of conservation and large scale production for commercial utilization were established successfully [92,93].

5. Safety evaluation

The safety of *Salacia* extracts is well documented and has been confirmed by in vitro genotoxicity studies. The potential genotoxicity and safety of *S. oblonga* extract evaluated with a standard battery of tests (reverse mutation, chromosomal aberrations and mouse micronucleus assay) did not produce any general organ or systemic toxicity when fed to rats at dietary concentrations as high as 2500 mg per kg body weight in a day based on mortality, clinical signs, ophthalmic findings, body weight changes, food consumption, and clinical and anatomic pathology toxicity assessments [94]. No deaths or abnormalities in gross pathological findings were observed during the safety profile of an extractive from *S. reticulata* trunk examination using an oral single dose toxicity test conducted on Sprague Dawley rats and chromosomal aberration test using cultured mammalian cells (Chinese Hamster Lung fibroblasts cells), suggesting that salacia extract has no severe acute toxicity or mutagenicity [95].

Though oral administration of the *S. reticulata* root extract (10 g per kg body weight) during early- (days 1-7) and mid-pregnancy (days 7-14) of Wistar rats had no effect on their fertility in terms of uterine implants, implantation index or gestation index; 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 [96]. Sikarwar and Patil have investigated the possible acute oral toxicity by *S. chinensis* extracts and confirmed that the administration of the stepwise doses of all the four extracts (ether, aqueous, chloroform and alcoholic extracts) of *S. chinensis* from 50 to 5000 mg per kg body weight caused no considerable signs of toxicity in the tested young female albino rats [60].

Safety evaluation of a hot water extract of *S. oblonga* supplemented to or processed into a medical food consumed for two weeks in amounts estimated at 10-fold greater than that proposed for human intake in male Sprague-Dawley rats, revealed no clinical chemistry or histopathologic indications of toxic effects [97].

6. Discussion and Conclusions

A large number of biologically active compounds have been isolated from *Salacia* species; however, their bioactive phytochemicals have not been well characterized. More efforts are needed to isolate new phytconstituents from these important medicinal plants. The plant extracts have been evaluated and used to treat a variety of ailments. Although the plant is being used commonly in most of the Ayurvedic

anti-diabetic formulations, the mechanism of action, except for α-glucosidases inhibitory activity, has not been studied at molecular and cellular levels. The fundamental understanding of biological and biochemical principles is required for future applications.

Due to the significant reduction in post-prandial blood sugar, serum triglycerides and low-density lipoprotein cholesterol levels among the human subjects, and enjoying little fat and rich protein and fiber contents without significant toxicity in the liver, kidney and intestine, the various species of dehydrated *Salacia* can be recommended as a useful ingredient in foodstuffs with additional benefits of their pharmacological properties, especially their anti-diabetic activity.

Though the safety of plant species has been well documented and has been confirmed by many toxicological studies, a reproducible (though weak), positive chromosomal aberration in human lymphocytes after *S. oblonga* extract intake [94] is of concern, and further toxicity research and clinical trials are recommended. In addition, understanding the drug interaction of *Salacia* with other therapeutic interventions through mechanistic studies is necessary.

Furthermore, due to the lack of proper cultivation practices, destruction of plant habitats, excessive and indiscriminate collection of these important medicinal plants for supplement of global demands, especially for its anti-diabetic property, they are severely threatened. Therefore, in order to sustain harvest and conservation, agronomic practices for cultivation have to be developed. Establishment of more proper protocols for in vitro propagation by advanced biotechnological methods of culturing plant cells and tissues is necessary as well. Approaches like genetic manipulation for hairy root culture, media standardization, and use of inducers/precursors of secondary metabolites could also be attractive.

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8. Conflict of interest

The authors report no conflicts of interest.

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