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Genus Salacia: A Comprehensive Review

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Abstract

Salacia sps (Family: Celastraceae / Hippocrateaceae) is an important source of chemicals of immense medicinal and pharmaceutical importance such as salacinol, mangiferin and kotanalol which are effective as antidiabetic, antiobese, hepatoprotective, hypolipidemic and antioxidant agent. Hence, this review considers the importance of the genus *Salacia* and an attempt is made to present macroscopical, phytochemical and pharmacological activities of the genus *Salacia*.

Key words: *Salacia sps*; Macroscopical; Phytochemical; Pharmacological activity

1. Introduction

Salacia is a climbing shrub, distributed in South – West India, Peninsula, Ceylon, Java, Thailand and Philippines [1]. Within India, it is distributed in Karnataka (rare in semi-evergreen forests of Western Ghats), Kerala (coastal forests of Kollam, Western Ghats of Pathanamthitta and Idukki districts) and Southern Orissa [2]. In the Traditional System of Medicine, the plants of this genus are being used as acrid, bitter, thermogenic, urinary, astringent, anodyne, anti-inflammatory, depurative, emmenagogue, vulnerary, liver tonic and stomachic. They are useful in vitiates conditions of vata, diabetes, hemorrhoids, inflammation, leucorrhoea, leprosy, skin diseases, amenorrhoea, dysmenorrhoea, wounds, ulcers, hyperhydrosis, hepatopathy, dyspepsia, flatulence, colic, and spermatorrhoea [3]. The present aim is to give a comprehensive review about macroscopical characteristics, phytochemical and pharmacological activities reported so far from this genus. The genus *Salacia* comprises of 100 species, out of which, in India, *Salacia reticulata* and *Salacia oblonga* are predominant species (4).

1.1 Taxonomical / Scientific Classification [5]

Kingdom: Plantae - Planta, plantes, plants, vegetal

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Subkingdom: Tracheobionta - vascular plants
Division: Magnoliophyta - angiosperms

Class: Magnoliopsida - dicots, dicotylédones, dicotyledons

Subclass: Rosidae

Order: Celastrales

Family: Celastraceae - bittersweet

Genus: Salacia

Species: reticulata;oblonga; campestris; hainanensis madagascariensis; chinesis; petensis; krausii; fruticosa; macrosperma

1.2 Macroscopical Description

The general macroscopical characteristics of the plants of the genus are as follows, scandent or sarmentosa shrub or small tree. Leaves usually opposite, petioled, coriaceous, shinning above, exstipulate. Flowers small, axillary or extra-axillary, fascicled or cymose, rarely solitary or 2-Nate. Calyx small, 5-partite. Petals 5, spreading, imbricate. Stamens 3 (very rarely 2 or 4), inserted on the disk, free or connate with the ovary; filament conniving at the apex, recurved; anthers small, dehiscing extrorsely, adnate, 2- celled, lobes divaricating at the base. Disk thick, sinuate, ovary sunk in the disk, conical, 3-celled; ovules 2, 4 or more in each cell, affixed to the axis, 1 or 2 seriate; style usually very short; stigma simple or 3 lobed. Fruit baccate, edible, 1-3 celled; cells 1-4 seeded; rind coriaceous or sub woody; pulp mucilaginous. Seeds large, angular; testa rather thick, coriaceous or fibrous; cotyledons thick, usually conferruminate [6, 7, 8].

1.3 Phytochemistry

Salacia species are known to elaborate anthocyanidines, catechins, phenolic acids, quinones, friedo-oleanones, quinonemethide and related triterpenoids (celastroloids), mangiferin, gutta percha and dulcitol. The major bioactive constituents are being xanthine, glucoside, mangiferin and two components with unique thiosugar structure sulfonium sulfate viz., salacinol and kotalanol. The phytoconstitutents isolated so far from different species of the genus is given below:

Sl No.	Species	Constitutents Isolated	Parts	Ref.
1.	*S. reticulata*	Mangiferin	Root	9
2.	*S. reticulata*	Kotanolol	Root and stem	10
3.	*S. reticulata*	(-)-Epicatechin; (-)-epigallocatechin; (-)-4'-*O*-methylepigallocatechin; (-)-epiafzelechin-(4ß → 8)-(-)-4'-*O*-methylepigallocatechin; (-)-epicathechin-(4ß → 8)-(-)-4'-*O*-methylepigallocatechin	Root	11
4.	*S. reticulata*	Salacinol	Root	12
5.	*S. reticulata*	Kotalagenin 16 acetate; 26-hydroxy 1,3 fridelanedione; maytenfolic acid; 3 β, 22β dihydroxy olean-12en- 29 oic acid	Root	13
6.	*S. reticulata*	Gutta-percha; sitosterol; pristimerin; epikokoondiol; salacenonal	Root bark	14,15
7.	*S. reticulata*	Salaciquinone	Root bark	16

8.	*S. reticulata*	Iguesterin; pristimerin; epikokoondiol	Stem bark	17
9.	*S. reticulata*	Isoiguesterinol; 30 hydroxy pristimerin; netzahualcoyene	Root bark	18
10.	*S. oblonga*	Salacinol; kotanolol; kotalagenin 16 acetate	Root	19
11.	*S. chinensis*	Leucopelargonidin; its dimmer,tetramer; dulcitol	Stem	20
12.	*S. chinensis*	Gutta; dimmer of leucopelargonidin	Leaves and stem	20
13.	*S. chinensis*	Fridel-1-en-3-one; friedelan-1,3,dione 7 α-ol; friedelan-1,3, dione-24 al; friedelan-1,3 dione; friedelan-1,3 dione,24 ol; friedelan-1,3 dione-24-oic acid; 24,25-oxidofriedelan-1,3 dione; 7, 24-oxidofriedelan-1,3 dione; 25,26-oxidofriedelan-1,3 dione	Root bark	21,22
14.	*S. fruticosa*	Friedelan-3-one-29al; friedelan3-one-29-ol; friedelin; friedel-1-en-3-one; amyrin; sitosterol	Root bark	21
15.	*S. macrosperma*	Saptarangi quinine A, B,C; salaciaquinonemethide; pristimerin; tingenone; hydroxytingenone; salaspermic acid	Root bark	23
16.	*S. chinensis*	Proanthocyanidin	Root	24
17.	*S. prenoides*	Triterpene	Root bark	25
18.	*S. madagascarienesis*	Isogusterin	Root	26
19.	*S. krausii*	28-nor-isoigusterin-17-carbaldehyde; 17-(methocarbonyl)-28-nor-isoiguesterin; 28-hydroxyiguesterin;celastrol; pristimerin;isoiguestrol	Root	27
20.	*Salacia species*	30-hydroxy friedelan3-on-28al	Root	28
21.	*S. campestris*	Maytenin; pristimerin	Root	29
22.	*S. petenesis*	Tingenone; netzahualcoyonal; 3-methoxy friedel-2-en-1-one; 29-hydroxy friedelan-3-one	Root	30
23.	*S. chinensis*	Salasone D and E; salaquinone B; salasol B	Stem	31
24.	*S. chinensis*	Salasone A,B,C; salaquinone A; salasol A; 3β, 22βdihyroxy olean-12-en—29-oic acid; tingenone; tingenin B; regeol A; triptocalline A; mangiferine	Stem	32
25.	*S. chinensis*	Salacinol	Stem	33
26.	*S. madagascariensis*	20-epi-isoiguesterinol; 6-oxo-isoiguesterin; isoiguestrin; isoiguesterinol	Root	34
27.	*S. hainanensis*	Friedelin; β-sitosterol; ursolic acid; mangiferin	Root	35
28.	*S. campestris*	Pristimerin; maytenin; 20-α-hydroxy maytenin; netzahualcoyene; salacin	Root bark	36
29.	*S. chinensis*	FoliasalaciosidesA1, A2, B1, B2, C, D, E1, F1, F2, F3, F4, F5, F6 and F7	Leaves	37

1.4 Pharmacological Activity

1.4.1 Antidiabetic Activity

The aqueous decoction of 40 plants were investigated for their hypoglycemic activity in Sprague-Dawley rats by Karunanayake and coworkers [38] for their ability to lower the fasting blood glucose level and improve the glucose tolerance in animals. Maximum reduction in blood glucose level (30%) was observed 3 hours after administration of *S.reticulata* aqueous decoction and which persisted up to 5 hours suggesting its hypoglycemic potential.

Serasinghe and coworkers demonstrated antidiabetic activity in streptozotocin induced diabetic rats. Reduction in plasma glucose levels were observed in 0.5 g/kg, 1.0 g/kg and 5.0 g/kg doses of *S.reticulata* by 42.8%, 45.4% and 87.5% respectively (39).

Shimoda investigated the effect of an aqueous extract of the stems of *S.reticulata* (SI) on post prandial hyperglycemia in rats and humans. In a dose dependent manner, SI extract suppressed an increase in serum glucose levels when fed with sucrose, maltose and starch. In addition, extract strongly inhibited the activities of α-glucosidase prepared from the yeast and rat jejunum with IC_{50} value of 5 and 8 μg/ml respectively. In the sucrose tolerance test, the aqueous extract of roots of *S.reticulata* (200 mg) given 5 minutes before sucrose loading (50 gm) significantly suppressed post prandial hyperglycemia in healthy human volunteers [40, 41].

Jayawardena and coworkers conducted a randomized double blind clinical trial to investigate the effect of an herbal tea containing *S.reticulata* in patients with type II Diabetes mellitus as assessed by HbA1C. A statistically significant fall in HbA1C was seen with tea compared to a rise in HbA1C with the placebo group which concludes that tea is an effective and safe treatment for type II diabetes [42].

Kajimoto and coworkers have investigated the effect of an aqueous extract from the stem of *S.reticulata* for the prevention of type 2 diabetes in a placebo controlled cross-over trial. There was significant reduction in fasting plasma glucose level, HbA1C and BMI suggesting the use of *S.reticulata* diet for individuals with mild type 2 diabetes [43].

Fig. 1: *Salacia oblonga*

Rabbani and coworkers have shown that hydro alcoholic extract of *S.reticulata* at the dose of 500 mg/kg p.o. reduced significantly the serum glucose level when compared to the control group in hydrocortisone induced hypoglycemia model [44].

Yoshikawa and coworkers discovered that a water soluble fraction (25-100 mg/kg per orally) prepared from the roots and stems of *S.reticulata* strongly inhibited elevated serum glucose level after the administration of sucrose or maltose. In addition, the fraction inhibited rat intestinal maltose and sucrose in *in vitro* test with IC_{50} value of 35 µg/ml and 26 µg/ml respectively [12].

To confirm this activity, Yoshikawa and coworkers performed a bioassay guided separation to isolate salacinol which showed competitive inhibition of intestinal α-glucosidase *in vitro*. The IC_{50} values were 3.2 µg/ml, 0.84 µg/ml and 0.59 µg/ml for maltase, sucrase and isomaltase respectively. The inhibitory action against maltase and sucrase was almost equal to that of acarbose (a clinically used α-glucosidase inhibitor) but more potent than acarbose against isomaltase. In addition to this, the inhibitory effect of salacinol on serum glucose levels in maltose and sucrose loaded rats were found to be more potent than that of acarbose [12].

Yoshikowa and coworkers further isolated kotanalol by bioassay guided fractionation which showed more potent inhibitory activity against sucrase. The IC_{50} values were 2.8 µg/ml, 0.58 µg/ml and 1.9 µg/ml for maltase, sucrase and isomaltase respectively [10].

Yoshikawa and coworkers further studied the inhibitory effect of mangiferin against carbohydrate metabolizing enzymes, sucrase, maltase, isomaltase, α-amylase and aldose reductase and compared it with salacinol and kotanalol. Magniferin inhibited α- glucosidase, sucrase, isomaltase and also aldose reductase activities which were not seen with kotanolol and salacinol. *S.reticulata* extract effectively inhibited α-amylase activity (derived from procaine pancreas) in a dose dependant manner with 68.55% inhibition at a concentration of 35µg/ml [11].

Minami and coworkers have demonstrated that desulfonated derivative of salacinol isolated from the roots of *S.oblonga* as a potent inhibitor of isomaltase with IC_{50} value of 0.64 mM [45].

In an animal model (KK-Ay mice) of type 2 diabetes, magniferin and its glucosides lowered blood glucose level at a dose of 30 mg/kg p.o. for two weeks and significantly improved hyperinsulinemia, which concluded that magniferin probably decreasse blood sugar level through decreasing insulin resistance [46].

Venkateswarlu and coworkers investigated the antidiabetic activity of various fractions of the alcoholic extract of the roots of *S.macrosperma* in alloxan-diabetic rats. The methanolic fraction followed by the residual fractionation of the alcoholic extract exhibited significant antidiabetic activity. This activity may be due to their insulin-like properties [47].

Pillai and coworkers have demonstrated the hypoglycemic activity of root bark of *S. prenoides* against alloxan induced diabetes in rats proving its potential as antidiabetic plant [48]. Augusti and coworkers have isolated two compounds from the root bark of *S.oblonga* from chloroform eluted fraction of the petroleum ether extract and a fluorescent compound which demonstrated about 60% and 76% hypoglycemic activity in comparison to an equal dose of tolbutamide (250 mg/kg) in albino rats. The results indicate the therapeutic importance of *S.oblonga* [49].

Matsuda and coworkers have evaluated the inhibitory activity of aqueous methanolic extract of roots of *S.oblonga* on increased serum glucose level in sucrose- and maltose-loaded rats. The water- and ethyl acetate-soluble portions from the aqueous methanolic extract showed inhibitory activities on α-glucosidase and aldose reductase respectively [19].

Krishnakumar and coworkers have studied the effect of petroleum ether extract of root bark of *S.oblonga* (SOB) in streptozotocin (STZ) diabetic rats. SOB prevented significantly the streptozotocin-induced hyperglycemia and hypoinsulinaemia suggesting that *S.oblonga* root bark extract possesses anti-diabetic activity [50].

Morikawa and coworkers have shown that six constituents viz., 3β, 22β-dihydroxyolean-12-en-29-oic acid, tingenone, tingenine B, regeol A, triptocalline A, and mangiferin, from *S.chinensis* were found to show an inhibitory effect on rat aldose reductase suggesting its antidiabetic potential [32].

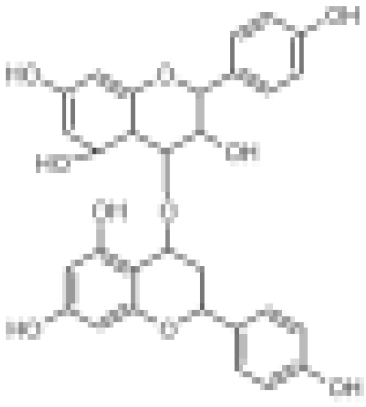
Yoshikawa and coworkers have studied the antidiabetogenic activity of methanolic extract from the stems of *S.chinensis* and showed potent anti-hyperglycemic effects in oral sucrose or maltose-loaded rats, inhibitory effects on intestinal α-glucosidase, rat aldose reductase, formation of Amadori compounds and advanced glycation end-products [33].

Matsuda and coworkers have studied the inhibitory effects on the intestinal digestion and absorption of sugar from health tea which is used for controlling diabetes. The duration of the inhibitory effect on the sucrose load of *S.oblonga* tea was found to be 110 min [51].

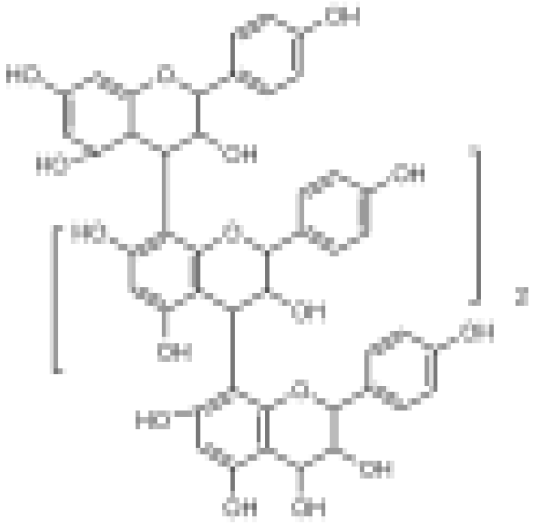
The effect of different doses of *S.oblonga* extract (0, 500, 700, or 1000 mg) on postprandial glycemic, insulinemic and breath hydrogen responses in healthy adults were studied by Heacock and coworkers. When compared with the control, the 1000 mg dose of *S.oblonga* extract reduced the plasma glucose and serum insulin (0 to 120 minutes postprandial) by 23% and 29% respectively. The other doses of *S.oblonga* extract did not have significant control on glycemia or insulinemia. Breath hydrogen excretion increased linearly as the dose of *S.oblonga* extract was increased [52].

Collene and coworkers studied the postprandial glycemic, insulinemic and breath hydrogen responses to a liquid nutritional product containing *S.oblonga* extract (100 mg; SOE) and two insulinogenic amino acids phenylalanine and leucine. *S.oblonga* extract was found to be a promising nutraceutical ingredient as it decreased glycemia (decrease in plasma glucose level and insulin level) and breath hydrogen excretion was 60% greater in the SOE-containing meals. Supplementation with amino acids had no significant additional effect on glycemia [53].

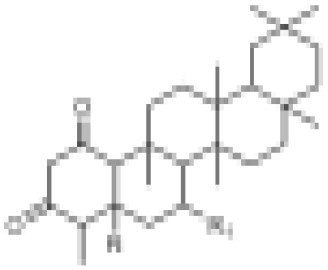
Li and coworkers have studied the effect of water extract of *S.oblonga* on the cardiac complications with diabetic patients on cardiac fibrosis and hyperglycemia in a genetic model of type 2 diabetes, the obese Zucker rats (OZR). Chronic administration of the extract markedly improved interstitial and perivascular fibrosis in the hearts of the OZR. It also reduced plasma glucose levels in non-fasted OZR; whereas it had little effect in the fasted animals, suggesting inhibition of postprandial hyperglycemia in type 2 diabetic animals which play a role in improvement of the cardiac complications of OZR [54]. *S.oblonga* root improves cardiac lipid metabolism in Zucker diabetic fatty rats (ZDF), a genetic model of type 2 diabetes and obesity by modulation of cardiac PPAR-alpha-mediated transcription of fatty acid (FA) metabolic genes was studied by Huang and coworkers. Chronic oral administration of *S.oblonga* extract (SOE) reduces cardiac triglyceride and FA contents and decreased the Oil red O-stained area in the myocardium of ZDF rats, which parallels the effects on plasma triglyceride and FA levels [55].



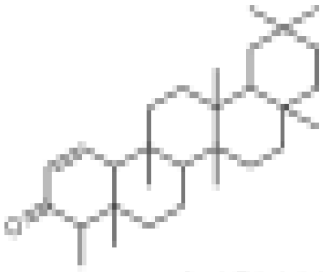
1 Leucopelargonidin dimer



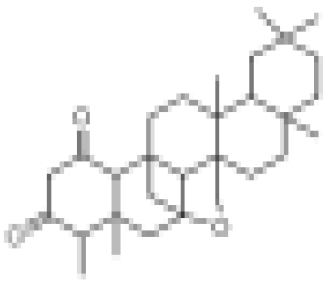
2 : Leucopelargonidin tetramer



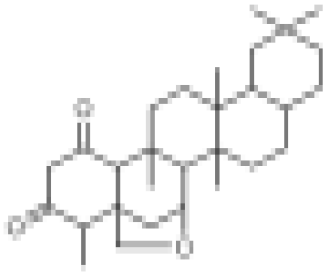
4 : R = Me,R1 = OH ; Friedelan-1,3-dione-7b-ol
5 : R = OH,R1 = H ; Friedelan-1,3-dione-[4 -a]
6 : R = COOH ,R1 = H ; Friedelan-1,3-dione-28-oic acid
7 : R = CH2OH ,R1 = H ; Friedelan-1,3-dione-24-ol



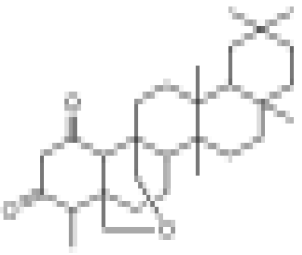
8 : 1-Friedel-1-en-3-one



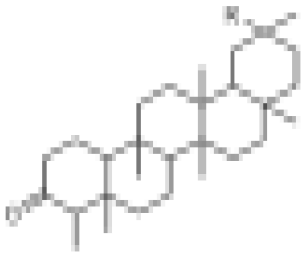
9 : 28,26-Oxidofriedelan-1,3-dione



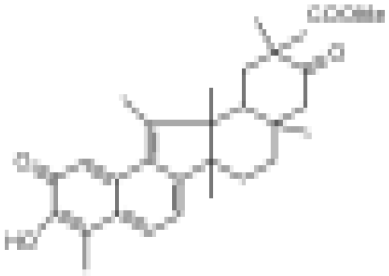
10 : 7,24-Oxidofriedelan-1,3-dione



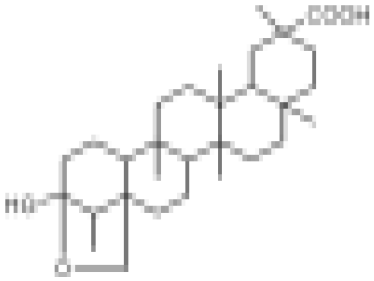
11 : 24,25-Oxidofriedelan-1,3-dione



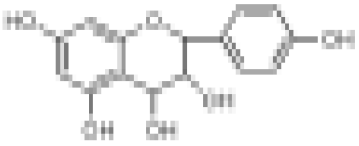
12 : R = CHO : Friedelan-3-one-28-al
13 : R = CH_2OH : Friedelan-3-one-28-ol



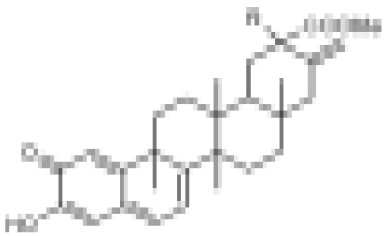
14 : Salacia quinonemethide



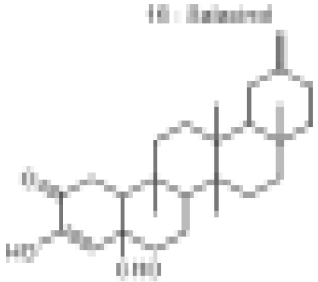
15 : Salaceronic acid



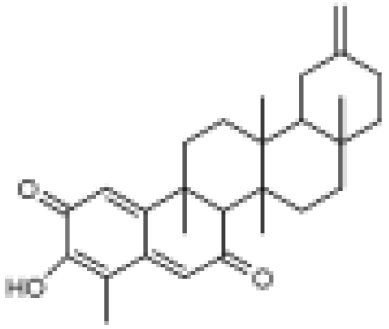
16 : Salacinol



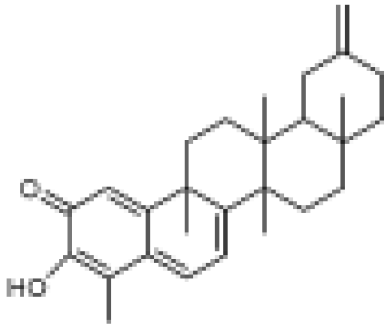
17 : R = CH_2OH : 30 Hydroxy pristimerin
18 : R = CH_3 : Pristimerin



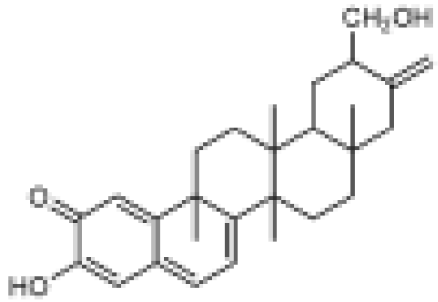
19 : Salaceronol



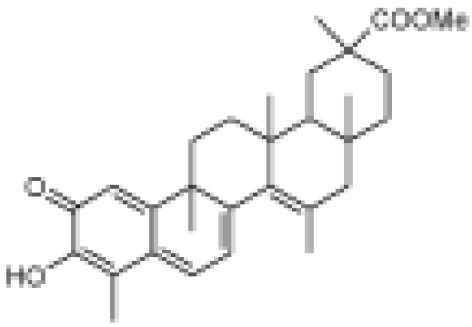
20 : Salaciaquinone



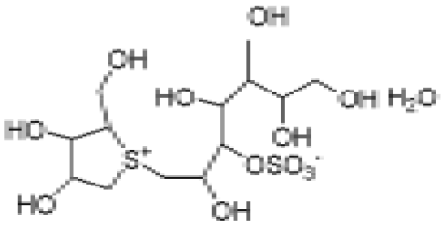
21 : Isoiguesterin



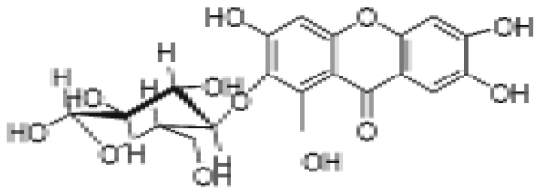
22 : Epikokoondiol



23 : Netzahualcoyene



Katallanol



Mangiferin

Furthermore, the treatment suppressed cardiac over expression of both FA transporter protein-1 mRNA and protein in ZDF rats, suggesting inhibition of increased cardiac FA uptake as the basis for decreased cardiac FA levels. These results suggest that SOE inhibits excess cardiac lipid accumulation and increased cardiac FA oxidation in diabetes and obesity which occurs by reduction of cardiac FA uptake, thereby modulating cardiac PPAR-alpha-mediated FA metabolic gene transcription [55].

Further the same workers have evaluated antidiabetic and antiobesity activity on chronic oral administration of the water extract of *S.oblonga* root in ZDF. The extract lowered plasma triglyceride and total cholesterol levels, increased plasma high-density lipoprotein levels and reduced the liver contents of triglyceride, non-esterified fatty acids and the ratio of fatty droplets to total tissue. These findings suggest that *S.oblonga* extract functions as a PPAR-alpha activator, providing a potential mechanism for improvement of postprandial hyperlipidemia and hepatic steatosis in diabetes and obesity [56].

Shimoda and coworkers have shown that an aqueous extract from *S.reticulata* when fed with commercial diet containing 0.05 or 0.1 % extract for 3 weeks lowered the serum triglycerides level which is attributed to decrease in absorption of sugar which is the source of triglycerides *in vivo* [57].

Willam and coworkers have studied the effect of *S.oblonga* extract (240 mg and 480 mg) on postprandial glycemia and insulinemia in patients with type 2 diabetes after ingestion of a high-carbohydrate meal. 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 to the control meal. The results suggest that *Salacia* may be beneficial for postprandial glucose control [58].

Huang and coworkers have investigated the effect of the water extract of *S.oblonga* (SOE) on obesity and diabetes-associated cardiac hypertrophy and discussed the role of modulation of cardiac angiotensin II type 1 receptor (AT(1)) expression in the effect. SOE treatment suppressed cardiac over expression of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and AT (1) mRNAs and AT (1) protein in ZDF rats. SOE (50-100 μg/ml) and mangiferin (25 μmol) suppressed angiotensin II-induced ANP mRNA over expression and protein synthesis in H9c2 cells. They also inhibited angiotensin II-stimulated [^{3}H] thymidine incorporation by cardiac fibroblasts which demonstrated that SOE decreases cardiac hypertrophy in ZDF rats at least in part by inhibiting cardiac AT(1) over expression [59].

Umamaheswari and coworkers have evaluated the antihyperglycemic effect of 'Ilogen-Excel' in streptozotocin induced diabetic rats. Oral administration of 'Ilogen-Excel' (50 mg/kg and 100 mg/kg) for 60 days resulted in significantly lowered levels of blood glucose and increased levels of plasma insulin, hepatic glycogen and total haemoglobin, decreased plasma thiobarbituric acid reactive substances, hydroperoxides, ceruloplasmin and vitamin E in diabetic rats. It was proved that combined therapy is better than individual therapy in STZ induced diabetic rats [60].

1.4.2 Hepatoprotective and antioxidant activity

The hepatoprotective effect of the hot water (SRHW) and methanolic (SRM) extracts from the roots and stems of *S. reticulata* were examined by Yoshikawa and coworkers using an oxidative stress-induced liver injury model. Both SRHW and SRM extracts (400 mg/kg, p.o.) significantly

suppressed the increase in glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activities in carbon tetrachloride (CCl_4) treated mice. These extracts also inhibited CCl_4 induced thiobarbituric acid reactive substance (TBARS) formation which indicates increased lipid peroxidation in the liver suggesting its hepatoprotective activity [61].

Rong and coworkers have demonstrated that an aqueous extract of *S.oblonga* root at the doses of 100, 300 and 900 mg/Kg, p.o. once daily for 28 days induced gender dependent hepatic hypertrophy in rats which is attributed to the sex hormones in both male and female rats. There was dose dependent increase in liver weight in both male and female rats but less predominant in female rats. It was found to activate PPAR-alpha in human hepatoma derived HepG2 cells by upregulation of PPAR-alpha and acyl-CoA oxidase in RNA expression [62].

1.4.3 Antioxidant activity

The antioxidative activity of mangiferin, (-)-4`-*O*-methylepigallocatechin and (-)-epicatechin-(4β——8)-(-)-4`-*O*-methylepigallocatechin from the roots of *S.reticulata* were examined. They showed potent scavenging activity of DPPH radicals and their IC_{50} values were 5.9, 10 and 3.2 μM respectively [61]. The free-radical scavenging activities of the quinonemethide triterpenes salacin, pristimerin, maytenin, 20 α-hydroxymaytenin and netzahualcoyene have shown 19, 20, 39, 28, 55 and 10 % inhibition of DPPH radical respectively was studied by Carvalho and coworkers [36].

Salaquinone B and catechin isolated from stems of *S.chinensis* have been reported to have radical scavenging activity against DPPH with 40 and 70 % inhibition respectively [31].

Krishnakumar and coworkers have shown that *S. oblonga* root (SOB) extract possess anti-lipid peroxidative activity in the cardiac tissue of streptozotocin (STZ) diabetic rats. SOB produced a significant decrease in peroxidation products viz., thiobarbituric acid reactive substances, conjugated dienes and hydroperoxides. The activity of antioxidant enzymes such as superoxide dismutase, catalase, GSHPxase and GSSGRase were increased in the heart tissue of diabetic animals treated with SOB suggesting its antioxidant activity [50, 81].

Nitric oxide production from lipopolysaccharide-activated mouse peritoneal macrophage and radical scavenging activities of the methanolic extract of *S. chinensis* which proved that it has potent antioxidant activity was studied by Yoshikawa and coworkers [33].

1.4.4 Antimicrobial activity

Antimicrobial activity of chloroform and methanolic extracts of *S.reticulata* were tested against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas auerginosa, Escheria coli* and fungal strains viz., *Cryptococcus neoformans, Candida tropicalis, Candida albicans* and *Epidermophyton floccosum* using zone of inhibition and MIC was reported by Choudhary and coworkers. It was observed that both extracts have inhibitory effects towards all microorganisms used in the test. However, chloroform extract was more effective than methanolic extract [63].

Samy reported the antimicrobial activity of the methanolic extract of *S.macrosperma*. It was found to be very effective against the test microorganism [64].

Deepa and Narmathabai have investigated the antibacterial activity of petroleum ether, ethyl acetate and chloroform extract of leaves and stems of *S.beddomei*. Ethyl acetate extracts was found to be most effective against all the tested organisms [65]. Setzer and coworkers have demonstrated the antibacterial activity of *S.petenensis* which led to the isolation of tingenone and netzahualcyenol as biologically active compounds against test microorganism used [30].

1.4.5 Cytotoxic activity

Setzer and coworkers has studied the cytotoxic activity of crude dichloromethane bark extract of *S.petensis*, which subjected to bioactivity guided fraction led to the isolation of tingenone and netzahyualcyenol. The possible mode of cytotoxic action of quinone-methide triterpenoids involves quasi-intercalative interaction of the compounds with DNA followed by nucleophilic addition of the DNA base to carbon-6 of the triterpenoid [30].

Augusti and coworkers have demonstrated the cytotoxic activity of petroleum ether extract of the root bark of *S.oblonga* against Ehrlich ascites tumor cells. The methanol eluted fraction of the petroleum ether extract (50 μg/ml) showed 100 percent cytotoxicity on Ehrlich ascites tumour cells [49]. Figueiredo and coworkers have shown that the compounds 28-nor-isoiguesterin-17 carbaldehyde, 17-(methoxycarbonyl)-28-nor-isoiguesterin, 28-hydroxyisoiguesterin, pristimerin and isoiguesterol isolated from the roots of *S.kraussii* by bioassay-guided fractionation have shown potent cytotoxicity in HT-29 cells (27).

1.4.6 Antiinflammatory activity

The anti-inflammatory activity of *S.oblonga* root bark powder was evaluated in male albino rats using carrageenan-induced rat paw oedema (acute inflammation) and cotton pellet granuloma (chronic inflammation) methods at a dose of 1000 mg/kg was studied by Ismail and coworkers. The increased acid and alkaline phosphatase activity and decreased serum albumin in cotton pellet granulomatous rats were normalized after treatment. The drug exerts their activity by antiproliferative, antioxidative and lysosomal membrane stabilization [66].

1.4.7 Antimalarial activity

Gessler and coworkers have studied forty-three different plant species for antimalarial activity against *Plasmodium falciparum in vitro*. The *in vitro* testing revealed that 37% of the investigated plants showed strong antimalarial activity with IC_{50} values below 10 μg/ml. The four most active plants included *Salacia madagascariensis, Cissampelos mucronata, Maytenus senegalensis* and *Zanthoxylum chalybeum* [67].

Figueredo and coworkers have isolated 28-nor-isoiguesterin-17-carbaldehyde, 17-(methoxycarbonyl)-28-nor-isoiguesterin, 28-hydroxyisoiguesterin, pristimerin and isoiguesterol from the roots of *S.kraussii* by bioassay-guided fractionation which showed antimalarial activity 30-50 fold greater than the extract itself [27].

1.4.8 Antiobese activity

Salacia is marketed as a Starch Blocker suggesting that it might help to reduce the body weight. The effects of a mixture of the *S.reticulata* aqueous extract and cyclodextrin (SRCD) on the development of obesity were examined by Kishino and coworkers by evaluating the effects of SRCD on the elevation of plasma triacylglycerol levels induced by oral administration of a high-fat (HF) liquid diet to male Sprague-Dawley rats. The plasma triacylglycerol concentration was significantly lower in the SRCD treated rats than in the control rats 4 h after HF diet administration. In an another study female C57BL/6 mice that consumed a solid HF diet containing 0.5% SRCD ad libitum for 8 week showed decrease in body weight and visceral fat mass than those fed with HF diet . In addition, the energy efficiency and the plasma leptin and adiponectin concentrations were lower in the mice that were administered SRCD than in those fed the HF diet alone. The inhibitory effects of SRCD on HF diet–induced obesity may be attributed to the inhibition of carbohydrate and lipid absorption from the small intestine [68].

Yoshikawa and coworkers studied the antiobesity effects of the hot water soluble extract (SRHW) from the roots of *S.reticulata* using obese rat models and an *in vitro* study. Body weight and periuterine fat storage in female Zucker fatty rats (8-9 week old) were suppressed by oral administration of SRHW (125 mg/kg) for 27 days. Furthermore, SRHW inhibited porcine pancreatic lipase (PL), rat adipose tissue–derived lipoprotein lipase (LPL) and glycerophosphate dehydrogenase (GPDH) activities with IC_{50} value of 264 mg/L, 15 mg/L and 54 mg/L, respectively. (-)-Epigallocatechin and (-)-epicatechin-(4ß---8)-(-)-4'-*O*-methylepigallocatechin isolated from the roots of *S.reticulata* inhibited PL activity with IC_{50} of 88 and 68 mg/L, respectively. (-)-Epicatechin, 3ß, 22ß-dihydroxyolean-12-en-29-oic acid and the tannin fraction inhibited LPL activity with IC_{50} of 81, 89 and 35 mg/L. Only the tannin fraction inhibited GPDH activity with an IC_{50} of 6.8 mg/L. The polyphenolic compounds may be involved in the antiobesity effects of SRHW in rats through inhibition of fat metabolizing enzymes (PL, LPL and GPDH) and enhanced lipolysis [69].

Recent pharmacological reviews have shown that *Salacia* roots modulate multiple targets for the improvement of type 2 diabetes and obesity-associated hyperglycemia, dyslipidemia and related cardiovascular complications seen in human and rodents [70].

1.5. Toxicity studies

1.5.1 Antigenicity and phototoxicity reactions

The antigenicity and phototoxicity of water soluble extract from *S.reticulata* (SRE) were examined by Shimoda and coworkers in guinea pigs. In a study of active systemic anaphylaxis reaction, neither the oral administration group (64 or 320mg/kg, 5 times/week, 3 weeks) nor the subcutaneous administration group (64mg/kg, 1 time/week, 3 weeks) exhibited any anaphylactic reaction. In a phototoxicity study, oral admini-stration of SRE (320 mg/kg) induced neither erythema nor edema. These results suggest that SRE is not antigenic or phototoxic [71].

1.5.2 Toxicological and cytogenetic assessment

The toxicity of *S.oblonga* root extract was evaluated in a sub chronic 90 days treatment in rats and was found to be safe as there was very less chromosomal abberrations in cultured rat peripheral blood lymphocyte *in vitro* after 90 days of treatment though the doses tested was 10 times more than the intended dose for humans [72].

1.5.3 Genotoxicity

S.oblonga root extract did not show any genotoxicity in number of tests like reverse mutation assay, chromosomal abberration assay, mouse micronucleus assay as recommended by US FDA with a very weak positive reproducible chromosomal abberration of human lymphocyte, though the dose used was 10 times more than the dose for human [73].

1.5.4 Contraindications and caution

A safety evaluation in animal models suggests that *Salacia* extract (both *S.reticulata* and *S.oblonga*) in doses 10 times what is suggested for humans for 14 days has no significant adverse reaction on blood chemistry, hematology or organ weights (74, 75, 76). Shimoda and coworkers showed no adverse effect on food intake, body weight, blood chemistry, organ weight or histopathological findings on rats fed with *S.reticulata* extract at doses upto 1000 mg/Kg for 13 weeks of continuous intake [77]. Animal study suggests only *S.reticulata* might adversely affect pregnancy with enhanced post-implantation losses, pups with low birth weight. However, the root extract was non-teratogenic. It can be concluded that the *S. reticulata* root extract can be hazardous to successful pregnancy in women and should not be used in pregnancy

complicated by diabetes as there are reports that mugs made of *S.reticulata* woods are available to be used routinely by diabetic patients to drink water [74].

1.5.5 Advers ereaction

Orally, *Salacia* can cause flatulence and distention. Flatulence is more significant with a 1000 mg dose compared to a 500 mg dose. Drinking *Salacia* tea can cause dyspepsia and loose stool [42].

1.5.6 Interaction with drugs

Salacia is thought to lower glucose levels. Combining *Salacia* with other antidiabetic drugs (glimepiride, glyburide, insulin, pioglitazone, rosiglitazone) that also lower blood glucose might have additive effect but increases the risk of hypoglycemia [78, 79].

1.5.7 Interaction with food, disease and other condition

Not known.

1.5.8 Dosage / Administration

Oral: For Diabeties, *Salacia* tea has been used three times daily before meals. *Salacia* in doses of 500 - 1000 mg in combination with meals has been also used [79, 80].

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