Guduchi (Tinospora cordifolia): Biological and Medicinal properties, a review

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Abstract

Guduchi (Tinospora cordifolia) is commonly known as rasayana plant and its rejuvenating property is well reported in Ayurvedic and other ancient literature. It is a fairly common plant of the dry deciduous forests growing over hedges and small trees. Various parts of the plant are being prescribed in Ayurveda and other systems of medicine as a monoherbal or polyherbal preparation. In India, various extracts of the plant are used as a remedy for many diseases and are included in various polyherbal preparations used for the treatment of diabetes, hepatitis, etc. Since each part of guduchi has some medicinal property, it is very much commercially exploitable. During the last few decades considerable progress has been achieved regarding its biological activity and medicinal applications. Hence, it can be chosen as a source for the development of industrial products for treatment of various diseases. We have put an effort to compile available literature on research work done for this plant mainly on its therapeutic utility till recent, from the early beginning. This review gives a bird view of the main biological activities, pharmacological actions and medicinal applications of guduchi extracts and also biological activities of few guduchi compounds isolated.

INTRODUCTION

Tinospora cordifolia (TC) is a large extensively spreading glabrous, perennial deciduous twiner with succulent stems and papery bark; leaves simple, alternate, cordate, entire, 7-9 nerved; flowers in clusters, female flowers usually solitary; fruits drupes, red when ripe. The surface of the stems appears to be closely studded with warty tubercles and the surface skin is longitudinally fissured. On removal of the surface skin the dark greenish mucilaginous stem is seen. The plant is sometimes cultivated for ornamental value and is propagated by cuttings. The leaves afford a good fodder for cattle ([1], [2]).

Ayurvedic literature quotes guduchi as a constituent of several compound preparations, used in general debility, dyspepsia, fever and urinary diseases. It has multiple actions like; stem is a bitter stomachic; stimulates bile secretion; causes constipation; tonic; allays thirst, fever, burning sensation, prevents vomiting; diuretic; enriches the blood; cures jaundice; useful in skin diseases; the juice is useful in diabetes, vaginal and urethral discharges, low fevers, and enlarged spleen (Ayurveda). The root and stem are prescribed in combination with other drugs as an antidote to snake bite and scorpion sting. An infusion of the powdered stem is used as an alternative and tonic and has enjoyed the reputation among ancient Hindu writers of being an aphrodisiac ([1], [2]).

IMMUNOMODULATORY ACTIVITY OF GUDUCHI COMPOUNDS

Guduchi is well researched for its immunomodulatory activities since many years; few compounds are being isolated and subjected for their possible mode of immunomodulatory activity. According to recent report, arabinogalactan polysaccharide (G1-4A) from the stem, appear to induce tolerance against endotoxic shock by modulation of cytokines and nitric oxide. In addition, it also modulates the release of nitric oxide by marine macrophages ([3]). The immunostimulating signaling mechanism of the novel (1, 4)-alpha-d-glucan reported to be through the activation of macrophages that occurs through TLR6 signaling, NF-kappa B translocation and cytokine production ([4], [5]).

Polysaccharide fraction from guduchi is found to be very effective in reducing the metastasis potential of B16F-10 melanoma cells ([6]). Arabinogalactan polysaccharide has good protective effect against iron mediated lipid peroxidation of rat brain homogenate as revealed by the thiobarbituric acid reactive substances and lipid

hydroperoxide assays ([7]) Arabinogalactan, a polyclonal mitogenicaly active compound is being isolated from the dried stem in the late nineties ([8]). Few more compounds cordioside, cordiofolioside A and cordiol are reported for macrophage activation ([9]).

PHARMACOLOGICAL ACTIVITIES OF VARIOUS EXTRACTS

Various pharmacological actions and medicinal uses of the different parts of plant are well reported in the ancient literature ([1] , [10] , [11]). Biological activities of the crude extracts as well as its different fractions from leaf, root, stem bark and fruit have been reported. The biological activities of crude extract(s) of various part(s) of guduchi on different animal models as well as on human beings have been discussed in the following section.

IMMUNOMODULATORY ACTIVITY

Guduchi has been referred as a plant of rasayana, which is being used as a rejuvenating herb in Ayurveda and other systems of medicine since many decades. Remarkable research work has been done on its immunomodulatory activity using its various extracts of different parts. Guduchi's immunomodulatory property as an adjuvant therapy in diabetic patients with foot ulcers has been reported. In a prospective double blind randomized controlled study lasting for over 18 months in 50 patients, produced significantly better outcome with improvement in wound healing, indicating beneficial effects of immunomodulation for ulcer healing ([12]).

The effect of alcoholic extract of whole plant on the proliferation and myeloid differentiation of bone marrow haematopoietic precursor cells in mice bearing transplantable Dalton's lymphoma is being studied. The extract is found to influence the myeloid differentiation of bone marrow progenitor cells and the recruitment of macrophages in response to tumor growth in situ ([13]). Immunostimulatory effect of leaf extract on (i) specific immunity (antibody response), (ii) non-specific immunity (neutrophil activity) and (iii) disease resistance against Aeromonas hydrophila is investigated in Oreochromis mossambicus. The leaf extracts have potential use as an immunoprophylactic to prevent diseases in finfish aquaculture ([14]).

The methanolic extract of TC has protective effect against shrimp viral pathogenesis, due to its immunomodulatory properties. The animal fed with extract showed less infection with white spot syndrome virus ([15]). The possible mechanism of action and effects of guduchi extract on antitumor activity has been extensively discussed. In vivo administration of the extract to mice bearing a spontaneous T cell lymphoma (Dalton's lymphoma) has been found to prevent tumor growth dependent regression of thymus and has been shown to upregulate antitumor activity of tumor associated macrophages ([16] , [17] , [18]). Anti-angiogenic activity has been reported using B16F10 melanoma cell induced capillary formation in animals. Intraperitoneal administration of the TC extract at a concentration of 20 mg/kg is found to inhibit the tumour directed capillary formation induced by melanoma cells significantly ([19]). The total extract, polar and non-polar extracts and the formulations containing guduchi exhibit promising immunomodulatory effect in cyclophosphamide treated mouse ascitic sarcoma ([20]).

Guduchi is being prescribed as a monoherbal as well as polyherbal formulation. The effect of polyherbal formulation containing TC has been reported for; cyclophosphamide induced genotoxicity in mice ([21]), favorable effect in patients with HIV infection ([22]) and immunomodulatory activity ([23]).

The extract of TC modulates hepatoprotective and immuno-stimulatory functions in carbon tetrachloride intoxicated mature rats (24). Rasayana herb TC has been studied extensively for its adaptogenic activity. The whole and aqueous extracts are having significant adaptogenic activity on a variety of biological, physical and chemical stressors on different animal models ([25]).

The effect of TC on the functions of macrophages obtained from mice treated with the carcinogen ochratoxin A has been investigated and the extract shows significant immunomodulatory response ([26]). Thatte et al. ([27]) has substantiated the immunomodulatory activity of aqueous extract by measuring the CFU-GM (Colony Forming Units of the Granulocyte Macrophage series) of mice and the extract increases CFU - GM activity in the serum significantly. Hepatoprotective herb TC increases the activity of the Kupffer cells in a chronic liver disease model using carbon clearance test as a parameter ([28]).

The phagocytic and killing capacities of neutrophils normalized only in patients receiving TC when tested on patients suffering from obstructive jaundice ([29] , [30]). The protective effects of the plant were comparable to gentamicin in E. Coli induced peritonitis. ([31]). The immunostimulant activity of TC is comparable with that of

Asparagus racemosus, glucan and lithium carbonate against the myelosuppressive effects of single and multiple doses of cyclophosphamide in mice ([32]).

ANTIHYPERGLYCAEMIC ACTION

Guduchi has been extensively studied for its hypoglycemic activity in support of its usefulness in the treatment of diabetes mellitus. The plant is being used for the treatment in the form of monoherbal or polyherbal formulation. An ayurvedic polyherbal formulation 'Ilogen-Excel', which contains TC as one of the constituent, administered at the dose of 50 mg/kg and 100 mg/kg for 60 days has shown significant decrease in the blood glucose levels and increase in the plasma insulin, hepatic glycogen and total hemoglobin ([33]). One more herbomineral formulation “Hyponidd” is reported for its possible hypoglycemic as well as antioxidant activity and the results are comparable with earlier reports on this plant ([34]).

The alcoholic root extract significantly reduces the blood and urine glucose, and lipids in serum and tissues in alloxan induced diabetic rats. The extract also prevents decrease in body weight ([35]). The extract of TC has no effect on amelioration of experimental diabetic neuropathy and gastropathy when tested on STZ induced diabetic mice and it produces significant decrease in plasma glucose concentration ([36]). Some of the investigators compared the hypoglycemic activity of vacuum dried 95% ethanolic extract with other well reported antidiabetic herbs on alloxan induced diabetic albino rats and the findings suggested that TC is a very potent hypoglycemic herb ([37]).

Diabetics are prone to the development of cataract; alcohol extract of TC has preventive effect on the development of cataract and produces a significant reduction of plasma glucose levels in alloxan induced diabetic rats ([38]). Renal hypertrophy and polyuria are the other complications of diabetes. Grover et al. ([39]) have investigated the effects of TC extracts on blood glucose concentrations as well as on kidney functions in streptozotocin induced diabetic rats. The extract when administered orally for 40 days was found to decrease plasma glucose concentration and prevented polyuria, rise in urinary albumin levels and renal hypertrophy as well.

The hypoglycemic effect of aqueous extract of TC has been tested at different time intervals from 21-120 days in mice. The extract at a dose of 400 mg/kg per day, exhibits a significant (70.37%) decrease in the plasma sugar level in mild diabetes (plasma sugar levels > 180 mg/dl, duration 21 days). But the hypoglycemic effect is decreased to 48.81 and 0% in moderate diabetes (plasma sugar levels > 280 mg/dl, duration 120 days) and severe diabetes (plasma sugar >400 mg/dl, duration 60 days) respectively ([40]).

Hyperglycemia and hyperlipidaemia coexists in diabetes. Hypoglycemic and hypolipidaemic activity of aqueous root extract of TC has been evaluated in the alloxan diabetic rats. The result showed a significant reduction in blood glucose and brain lipids, also induced an increase in body weight, total haemoglobin and hepatic hexokinase. TC also decreased hepatic glucose-6-phosphatase and serum acid phosphatase, alkaline phosphates and lactate dehydrogenase ([41]). In another study, it significant reduced serum and tissue cholesterol, phospholipids and free fatty acids at the dose of 2.5 and 5.0 g/kg body weight for 6 weeks ([42]). It is interesting to note that, the aqueous, alcoholic and chloroform extracts of the TC leaves has significant hypoglycemic activity, which is postulated to be an insulin like action and it has no significant hypolipidaemic activity ([43]).

Some authors correlated the hypoglycemic activity of polyherbal formulation “Trasina” to the superoxide dismutase (SOD) activity of pancreatic islet cells in the STZ induced diabetic rats. They reported that, the formulation induces a dose related decrease in hyperglycemia and augments islet SOD activity ([44]). Effect of TC on fasting blood sugar level, glucose tolerance and enaline induced hyperglycemia were studied in the late sixties and the results found were promising ([45]).

ANTIOXIDANT/HEPATOPROTECTIVE ACTIVITY

Hepatoprotective activity of various parts of guduchi is very well documented. Many monoherbal as well as polyherbal formulation(s) have been marketed for the treatment of various liver diseases. Protective effect of TC's crude extract on drug induced liver injury and immunosuppression by isoniazid, rifampicin and pyrazinamide is documented recently. Crude extracts of TC aerial roots has protective action against liver injury induced by the above mentioned anti-tubercular drugs and it prevents immunosuppression. It is suggested that consumption of hepatoprotective herbs like TC with the above said drugs can minimize the liver toxicity ([46]). Pepticare, a herbomineral formulation which contains guduchi has antiulcer and antioxidant activity. This formulation at a dose of 125, 250, 500 and 1000 mg/kg, p.o produces a significant antiulcer activity in the pylorus ligated

rat model. It is postulated that antioxidant mechanism of the formulation is responsible for the possible anti ulcer activity ([47]). One more polyherbal formulation has hepatoprotective effect on a day-old broiler chicken in paracetamol induced hepatic injury ([48]). The well known antioxidant mechanism of TC is being extrapolated to its neuroprotective activity. The herb exhibits significant protective effect in rat hippocampal slices subjected to oxygen and glucose deprivation and also has strong free radical scavenging properties against reactive oxygen and nitrogen species as studied by the electron paramagnetic resonance spectroscopy ([49] , [50]).

Alcoholic root extract has antioxidant defence mechanism in alloxan induced diabetic rats. It is reported that the extract normalizes the antioxidant status of heart, brain, liver and kidney at a dose of 100 mg/kg orally for six weeks and the effect is more prominent than glibenclamide and insulin ([51] , [52]). The possibility of using proven antioxidant herb guduchi for the ischemic brain damage has also been reported. The herb has strong free radical scavenging properties against reactive oxygen and nitrogen species as revealed by electron paramagnetic resonance spectroscopy, diminishing the expression of iNOS gene, therefore attenuating oxidative stress mediated cell injury during oxygen glucose deprivation and exerting the above effects at both the cytosolic as well as at gene expression levels. Hence TC may be an effective therapeutic tool against ischemic brain damage ([49] , [50] , [53]).

“HIMOLIV” a polyherbal formulation is claimed to be useful in hepatitis, jaundice and biliary dysfunction. It produces protective effect on the carbon tetrachloride and paracetamol induced liver necrosis at the dose of 0.5 and 1.0 ml/kg, p.o ([54]). One more polyherbal formulation “HP-1”, possess strong hepatoprotective and antioxidant activity, when administered orally ([55]). Aqueous root extracts causes a significant reduction in thiobarbituric acid reactive substances and an increase in reduced glutathione, catalase and superoxide dismutase activity in alloxan induced diabetic rats. This effect was found to be more than glibenclamide ([56] , [57]). Extract of TC prevents the toxic effects produced in mice hematological system attributed to the free radical generated due to the administration of cyclophosphamide ([58]).

CYTOTOXIC EFFECT

Guduchi is very well established immunomodulatory agent and proven antioxidant herb. Its main usefulness in the traditional system of medicine is based on these mechanisms. The anti tumor activity of TC may be due to decreased lipid peroxidation, glutathione-S-transferase activity or due to the release of lactate dehydrogenase. Dichloromethane extracts of TC shows concentration dependent decline in the clonogenicity, glutathione-S-transferase activity as well as increase in lipid peroxidation with a peak at 4 h and a lactate dehydrogenase release with a peak at 2 h ([59]). In Ehrlich ascites carcinoma bearing mice, the highest number of survivors were observed at an optimal dose of 50 mg/kg in dichloromethane extract of TC ([60]). The hydroalcoholic extract of aerial parts has potent chemopreventive effect against cancer, in which oxidative stress plays an important causative role ([61]).

In vivo administration of alcoholic extract to mice bearing a spontaneous Dalton's lymphoma prevented the tumor growth dependent regression of thymus. This extract, augmented the proliferation of thymocytes with a concomitant decrease in thymocyte apoptosis ([17]). Methylene chloride extract is more potent than the methanol and aqueous extracts in preventing the cell killing in cultured HeLa cells. The effect was found to be high at a dose of 100 µg/ml and effects of methanol and aqueous extracts are almost identical ([62]).

CARDIOPROTECTIVE ACTIVITY

Many antioxidative plants are shown to be cardioprotective in experimental models of myocardial ischemia reperfusion injury. A dose dependent reduction in infarct size and in lipid peroxide levels of serum and heart tissue has been reported with ethanol extracts of TC at various doses ([63]). The cardioprotective activity of an herbal formulation “Caps HT2”, which contains methanol extract of TC as a component, has antioxidant, anticoagulant, platelet antiaggregatory, lipoprotein lipase releasing, anti-inflammatory and hypolipidaemic activity in rats ([64]). Administration of 2.5 and 5.0 g/kg body weight of aqueous root extract for 6 weeks results in a significant reduction of serum and tissue cholesterol, phospholipids and free fatty acids in alloxan induced diabetic rats ([42]).

OTHER ACTIONS

The usefulness of TC as a cognitive enhancer is substantiated by its potent in vitro acetylcholinesterase inhibitory activity. Methanolic and successive water extracts have been investigated, whereby, methanolic extract was found to be more active than water extract ([65]). The adjuvant immunomodulatory effect of the TC's aqueous extract in combination with chloroquine was studied for the

treatment of hyper reactive malarious splenomegaly. Addition of extract to chloroquine had regression of spleen by 37-50% after six weeks and 45-69% after six months from the start of the treatment. Likewise decrease in IgM and increase in Hb as well as wellbeing were observed ([66]). The efficacy of the extract in patients of allergic rhinitis was assessed in a randomized double blind placebo controlled trial which demonstrated a significant decrease in all the symptoms of allergic rhinitis ([67]).

Methanolic (70%) stem extract has significant male antifertility activity. In male rats, it has no effect on body weight loss but decreases the weight of testes, epididymis, seminal vesicle and ventral prostate in a significant manner. It reduces the sperm motility as well as sperm density significantly, which result in reduction of male fertility by 100% ([68]).

TC affords protection against gamma irradiation in mice. This property can be exploited to human applications for radioprotective manifestation. A preparation of TC administered to mice at a dose of 200 mg/kg b.w. and an aqueous extract at 5 mg/kg b.w. 1 hour before whole body gamma irradiation, exhibits a significant protective effect ([69] , [70]). Goel et al. ([71]) have reported that the direct and indirect antioxidant actions of TC acts in corroboration to manifest the overall radioprotective effects.

A crude extract formulation containing TC produces cure rate of 73% at a dose of 800 mg/kg/day in hepatic amoebiasis. The ethanolic extract alone and in combination as a polyherbal crude extract has antiamoebic effect against Entamoeba histolytica. The result of the crude polyherbal formulation is significant as that of metronidazole ([72] , [73]). It has in vitro phagocytic and microbicidal activity of a monocyte-macrophage cell line on Candida species organisms at a dose of 100 mg/kg ([74]). The diuretic activity reported by Nayampalli et al. ([75]) was comparable to hydrochlorothiazide. The TC stem's hexane and chloroform soluble portions showed insignificant antipyretic activity in rabbits receiving subcutaneous yeast injections ([76]).

CONCLUSION

Guduchi, popularly known as amruth in Ayurveda is a unique source of various types of compounds having diverse structure. Remarkable research has been done on the biological activity and possible application of these compounds and still extensive investigation is needed to exploit their therapeutic utility to combat various diseases. A systematic research should be undertaken to develop a modern drug using compounds isolated from guduchi. However, various crude extracts from various parts of guduchi have medicinal application from time immemorial. A modern drug can be developed after extensive investigation of its pharmacodynamics, kinetics and proper standardization and clinical trials. Quite a significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts. Some more therapeutically useful preparations can be marketed, which generates enough encouragement among the scientists in exploring more information about this plant. An extensive research should be undertaken on guduchi plant and its products including standardization of various guduchi parts and subparts and drug development program using guduchi compounds for their better economic and therapeutic utilization.

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