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Giloy (Tinosporia cordifolia): A Review for its hepatoprotective effects, safety profile and terms and conditions for medicinal use.

Author- Dr Dattu D. Karande M.D.(Ayu.) Assistant professor, Department of Dravyaguna vigyan, Aditya Ayurved college, Beed (Maharashtra)

Abstract- Giloy *(Tinospora cordifolia)* is Herbal drug of traditional system of medicine. The common names are Amrita and Guduchi and belong to the family of Menispermaceae. It is considered an essential herbal plant of Indian system of medicine (ISM) and has been used in the treatment of fever, urinary problem, dysentery, skin diseases leprosy, diabetes, and many more diseases. In this article, we have reviewed the literature on the Hepatoprotective effect, saftey profile and terms and conditions for medicinal use of *Tinospora* cordifolia and critically analyzed to provide perspectives and instructions for future research.

Key words – Guduchi, Hepatoprotective, safety,

Introduction

Earlier in the twentieth century, herbal medicine was the prime medication system as antibiotics or analgesics were not available. Increasing use of an allopathic system of medicine due to its fast therapeutic action and herbal medicine gradually lost their popularity among the people.

Giloy (Tinospora cordifolia) is one of the plant that Acharya charaka and Acharya Vaghbhata mentioned in Aagryasangraha, Agrya Sangraha means collection of leading or principle substances. *T. cordifolia* is a miraculous plant that belongs to the family Menispermaceae. It is also known by diverse names Guduuchi, Guduuchikaa, Guluuchi, Amrita, Amritalataa, Amritavalli, Chinnaruuhaa, Chinnodbhavaa, Madhuparni, Vatsaadani, Tantrikaa, Kundalini, Guduchi sattva in Ayurveda, and Giloya in folk. Furthermore, this plant is also known as the herbal ingredient of "soma" or "heavenly elixir" (food for immortals, mentioned in Rigveda) altogether more than 100 herbal ingredients. *T. cordifolia* is also known as ''nectar of life'', as it strengthens the immune system of the body and maintains the functions of various organs in harmony. *T. cordifolia* is a large, glabrous, deciduous, climbing shrub found in the tropical region of India, Andamans, China. The structure of the stem is fibrous and the transverse section exhibits a yellowish wood with radially arranged wedge-shaped wood bundles, containing large vessels, separated by narrow medullary rays. It has creamy-white to grey bark, deeply left spirally and the stem contains rosette-like lenticels. The leaves are membranous and cordate in shape. Flowers are in axillary position, 2–9 cm long raceme on leaflet branches, unisexual, small, and yellow. Male flowers are clustered and female is usually solitary. The seeds are curved. Fruits are fleshy and single-seeded. Flowers grow during the summer and fruits during the winter.

Now a days due to multiple benefit's of Giloy (Tinospora cordifolia) specially immunomodulatory effects people's are using this herbs widely, due to lack of information about this plant people consuming without medical supervision and hence they get harms instead of benefits. In this article review of hepatoprotective action , saftey profile, and terms and conditions for medicinal use was performed and presented systematically.

Materials and methods

Electronic search on worldwide accepted scientific databases (Google Scholar, Science Direct, SciFinder, Web of Science, PubMed, Wiley Online Library, ACS Publications Today) was performed to compile the relevant information. Some information was obtained from books, database on medicinal plants used in Ayurveda, and herbal classics books written in various languages.

Hepatoprotective Activity- Liver diseases are becoming a major public health concern. Epidemiologic data report that the prevalence has been sharply increasing during the past 2 decades globally. The data from the 2017 Global Burden of Disease study show an average of 2.14 million liver-related deaths, worldwide.

In an interesting human study done at the Department of Gastroenterology Surgical Services, Seth G.S. Medical College in Bombay, India the effect of Percutaneous Transhepatic Biliary Drainage (PTBD) was studied. PTBD is performed in surgical jaundice to decompress the biliary tree and improve hepatic functions. However, the risk of sepsis is high in these patients due to immunosuppression and surgical outcome remains poor. Therefore an efficacious alternative treatment could significantly change the outcome of such a condition. Researchers set up four groups of patients. The first two groups were (A) those undergoing surgery without PTBD (n = 14), and (B) those undergoing surgery after PTBD (n = 13). The mortality was 57.14% in Group A as compared to 61.54% in Group B. Serial estimations of bilirubin levels carried out during the course of drainage (3 wks) revealed a gradual and significant decrease. Antipyrine half-life did not change significantly. The phagocytic and intracellular killing (ICK) capacities of neutrophils remained suppressed. Thus PTBD did not improve the metabolic capacity of the liver and mortality was higher due to sepsis. Group (C) patients received Guduchi during PTBD (n = 16) and Group (D) patients received Guduchi without PTBD (n = 14). A significant improvement in neutrophil function occurred by 3 weeks in both groups. The mortality in Groups C and D was 25% and 14.2% respectively during the preoperative period. There was no mortality after surgery. It appears from the results of this study that immune function as reflected by neutrophil function play an important role in influencing prognosis and that an improvement in immune function by Guduchi offers marked potential for enhanced survival .[1]

In a similar study at the Department of Pharmacology, Seth G S Medical College in Bombay, the effect of T. cordifolia was evaluated on surgical outcome in patients with malignant obstructive jaundice. Thirty patients were randomly divided into two groups, matched with respect to clinical features, impairment of hepatic function (as judged by liver function tests including antipyrine elimination) and immunosuppression. Group I received conventional management, i.e. vitamin K, antibiotics and biliary drainage; Group II received T. cordifolia (16 mg/kg/day orally) in addition, during the period of biliary drainage. Hepatic function remained comparable in the two groups after drainage. However, the phagocytic and killing capacities of neutrophils normalized only in patients receiving Tinospora. Post-drainage bactobilia was observed in 8 patients in Group I and 7 in Group II, but clinical evidence of septicemia was observed in 50% of patients in Group I and none in Group II ($p < 0.05$). Post-operative survival in Groups I and II was 40% and 92.4% respectively ($p < 0.01$). Researchers noted that Guduchi appears to improve surgical outcome by strengthening host defenses (Rege and others 1993).

HepatoProtective Effects of *Tinospora cordifolia* water extract (TCE) on Hepatic and Gastrointestinal Toxicity was reported by Sharma *et al.*, a significant increase in the levels of gamma-glutamyl transferase, aspartate transaminase, alanine transaminase, Triglyceride, Cholesterol, HDL and LDL ($P < 0.05$) in alcoholic sample whereas their level get downregulated after TCE intervention, patients showed the normalized liver function of *T. cordifolia* stand to relieve the symptoms [2]

Animal study conducted on Swiss albino mice Polyherbal extract at 500 mg/kg body weight exhibited a significant ($P < 0.05$) hepatoprotective activity as compared to paracetamol group was reported by Dewasya Pratap Singh et al. [3]

The study was carried out at the Animal House facility of Bharati Vidyapeeth Deemed University's Medical College (Maharashtra, India). Satwa from T cordifolia had a specific action in maintaining the lipid profile: total cholesterol, high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein. Improvement in the hepatic function, normalization of the lipid profile in the serum and liver.[4]

Animal study conducted on Albino Wistar rats to evaluate Hepatoprotective action of T cordifolia. ALT, ALP & Total bilirubin levels were significantly Decreased in group treated with T cordifolia, It can be concluded from the present study that T. cordifolia extract is a potent hepatoprotective agent. It is assumed that this hepatoprotective effect

of T. cordifolia may be due to several reasons such as antioxidant and/or free radical scavenger property and ability to induce hepatic regeneration.[5]

The hepatoprotective action of *T. cordifolia* was reported in one of the experiment in which goats treated with *T. cordifolia* have shown significant clinical and hemato-biochemical improvement in CCl_4 induced hepatopathy. Extract of *T. cordifolia* has also exhibited in vitro inactivating property against Hepatitis B and E surface antigen [6]

The study was conducted to evaluate the hepatoprotective activity of different extracts of Tinospora cordifolia against carbon tetrachloride (CCl4) induced liver damage in rats. Ethanolic extract of T.cordifolia showed significant hepatoprotec-tive effect by reduction in serum enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TBL) in the selected model which is followed by aqueous and pet ether extracts.[7]

Effect of Tinospora cordifolia extract on modulation of hepatoprotective and immunostimulatory functions in carbon tetrachloride (CCl_4) intoxicated mature rats is reported by Biswadev bishayi et al. treatment with T. cordifolia extract (100 mg/kg body weight for 15 days) in CCl_4 intoxicated rats was found to protect the liver, as indicated by enzyme level in serum. A significant reduction in serum levels of SGOT, SGPT, ALP, bilirubin were observed following T. cordifolia treatment during CCl_4 intoxication.[8]

Kupffer cells are major determinants of outcome of liver injury. Their activity was therefore studied in a model of chronic liver disease. The effect of Tinospora cordifolia, an indigenous agent with proven hepatoprotective activity, was evaluated on Kupffer cell function, using carbon clearance test as a parameter. Rats were divided into two major groups. In Gp I which served as normal control t1/2 of carbon was 9.48 +/- 4.14 min. GpII received horse-serum in a dose of 0.5 ml/100 gm b.w. i.p. for a period of 12 weeks and was divided into three sub-groups. In Gp IIA at the end of 12 weeks half-life of carbon was found to be significantly increased to 19.86 +/- 7.95 min ($p < 0.01$). Indicating suppressed Kupffer cell function in chronic liver damage. In Gp IIB treated with vehicle for 4 more weeks there was significant prolongation of half-life to 38.32 +/- 10.61 min ($p < 0.01$), indicating perpetuation of damage in absence of damaging agent. Whereas in Gp IIc, treated with Tinospora cordifolia t 1/2 was decreased to 14.24 7.74 min ($p < .01$), as compared to vehicle control indicating a significant improvement in Kupffer cell function and a trend towards normalization.[9]

The importance of Tinospora cordifolia stem and leaves extract was investigated for its possible hepatoprotective effect in Swiss albino male mice against lead nitrate induced toxicity. Administration of aqueous stem extract (400 mg/kg body weight, orally) and aqueous leaves extract (400 mg/kg body weight, orally) along with the lead nitrate (5 mg/kg body weight, i.p. for 30 days) increased the activities of SOD and CAT and decreased the levels of AST, ALT, ALP, and ACP enzymes in mice. These biochemical observations were supplemented by histopathology/histological examinations of liver section. Results of this study revealed that plant extract could afford protection against lead-induced hepatic damage.[10]

Saftey profile

Guduchi ghana vati- an open-label randomized controlled pilot study with a sample size of 30 participants (15 in each arm). The participants were asymptomatic or mild to moderate cases of COVID-19. Guduchighan Vati 500 mg twice daily for 10 days was administered in the intervention group as standalone therapy and Hydroxychloroquine in the control group. Guduchighan Vati is a safe and effective treatment for asymptomatic and mild cases of COVID-19 and it lowers the time to RT-PCR negative status without any adverse drug event.[11]

Aqueous extract- The study was aimed to evaluate the safety profile of Tinospora cordifolia in healthy volunteers using a battery of haematological, and biochemical tests and open questionnaire method. Thirty healthy volunteers (males - 22 and females - 8) aged 18 - 30 years (mean 22.5 ± 0.28) who volunteered to participate were studied in a randomized, double - blind, placebo controlled design. The volunteers were provided with 21 days of medication (coded box) containing Tinospora cordifolia 500 mg or matching placebo. One tablet of Tinospora cordifolia of 500mg strength or placebo was taken once daily orally in the morning along with breakfast for 21 days. The safety assessment was done with the help of haematological and biochemical investigations which were assessed before and after the medication by unpaired t test. 'Unpaired t test' using SPSS computer software package. Analysis of the various lab values between the control and the test group before and after taking the drug/placebo by unpaired

't' test shows no significant difference between the groups (p = > 0.05).Hence it can be concluded that Tinospora cordifolia is safe at a dose of 500mg per day for a period 21 days in healthy volunteers for the parameters studied.[12]

Toxicity studies revealed no noteworthy toxic or adverse effects for Tinospora cordifolia extracts up to the highest oral doses of 1.6 g/kg.[13].

In an experimental study to evaluate the genotoxic risk of the aqueous extract of T. cordifolia (TC) in a battery of four different genotoxicity tests viz., Ames, in vitro chromosome aberration (CA), rodent bone marrow micronucleus (MN), and Comet assay. Experimental results confirmed that in Ames test up to 5000 microg/plate of TC did not exhibit any mutagenic effect in Salmonella typhimurium mutant strains (TA97a, TA98, TA100, TA102, and TA1535). In CA assay, TC was not clastogenic to human peripheral blood lymphocytes up to a concentration of 3000 microg/ml. In MN and Comet assays, TC was pre-treated for 7 days at three dose levels (150, 200 and 250 mg/kg body weight) orally to male Balb/c mice. The results showed that TC treatment did not display clastogenicity and DNA damaging effect in bone marrow erythrocytes and peripheral blood lymphocytes respectively.[14]

Terms and condition for medicinal use-

In Ayurvedic therapeutics, drug therapy is given prime importance. There is a very well developed sub-discipline entirely devoted to drug formulations known as “Bhaisajya Kalpanaa”. five basic forms of formulation known as 1- ‘Swarasa’ the expressed juice, 2-‘Kalka’, a fine paste obtained by grinding fresh or wet grinding dried plant material 3- ‘Kwaatha’, the decoction, 4- ‘Sheeta’ or ‘Hima’, the cold water infusion and 5- ‘Faanta’, the hot water infusion. Proper time for administration of *Aushadha* is known as *Bhaishajya Kaala*. *Bhaishajya Kaala* are the essential tools for administration of *Aushadha*, negligence may lead to the grave deficit in the treatment. All therapeutic measures administered to treat a disease even though wholesome and skillfully given, fail to cure it, if they are used in lesser or in excessive dose or at wrong time or in wrong manner. If appropriate therapy is administered in appropriate manner it certainly cures the disease.[14]

In context to Giloy (Tinospora cordifolia) and all Ayurvedic herbs the following things should remember before using the herbs for medicinal purpose.

1) Drug identification
2) Drug dose
3) Drug administration time
4) Total duration of drug administration
5) Forms of drug at the time of administration
6) Site of collections
7) Time of drug collection
8) Anupan
9) Contraindication
10) Used only under medical supervision.

Discussion- Medicinal plants are the reservoir of wide arrays of the majestic secondary metabolites, which can treat severe diseases. Medicinal plants are the blessings by nature to humankind on this earth. Secondary metabolites developed into more effective and less toxic medicines. India is sitting on the goldmine of traditionally well-practiced and well-reported knowledge of the medicinal system. India is bestowed with an enormous diversity of plants on this earth due to it is rightly called a ‘‘botanical garden of the world’’

Giloy (Tinospora cordifolia) is the one of the Rasayan dravya explained in ancient literature and widely used in many formulations. In present study three clinical trial conducted by well known institute suggesting that Giloy poses hepatoprotective activity and more than three experimental study also suggests its hepatoprotective activity. Safety profile of Giloy when used in the form of Ghana Vati it is safe for 10 days at an dose of 500mg twice daily, another study conducted for saftey evaluation of Giloy extract at an dose of 500mg once daily suggest that Giloy is safe for 21 days. The highest dose of aqueous extract of Giloy is 1.6 gm/kg also safe. After analysing data obtained from various authenticated clinical and experimental study it is considered that Giloy is safest drug.

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