Int J Trans Res Ind Med 2022, 4(1): (P) 01 - 12

Review Article

ISSN 2582-0109

International Journal of Translational Research in Indian Medicine
www.ijtrim.com
Volume 4, Issue 1 – 2022

AMRITHA (TINOSPORA CORDIFOLIA) FOR PREVENTION OF VIRUS INFECTIONS AND CANCER THRU IMMUNE STIMULATION

Cheppail Ramachandran [*1], Karl-Werner Quirin[2], Steven J. Melnick [1]

[1]*Dharma Biomedical LLC, Miami, Florida 33155, United states*

[2]*Flavex Naturextrakte GmbH, Rehlingen 66780, Germany*

ABSTRACT

In this review paper we describe the medicinal properties of Amritha (Tinospora cordifolia) especially for strengthening the innate immune system and preventing pathogenic infections and cancer. Even though Amritha has been described in ancient Ayurvedic books and Hindu mythology, its medical relevance has not been fully exploited in the world to date. The herbal importance of Amritha is very much relevant during the current COVID-19 pandemic due to its significance for improving innate immunity by increasing the activities of cytotoxic T cells and natural killer cells in the body. In addition to immunological significance, each part of this important medicinal plant has beneficial effects on several human diseases. The ethnobotanical and traditional medicine descriptions of Amritha would help to isolate and characterize pharmaceutically important principles from it contributing to the drug discovery programs

KEY WORDS: ***Amritha, Tinospora cordifolia, Immune stimulation, Natural killer cells, Cytotoxic T cells, medicinal properties, phytochemicals, nutraceutical, virus infections***

Corresponding Author: Cheppail Ramachandran, Dharma Biomedical LLC, Miami, Florida 33155, United states

1. Introduction

The overwhelming majority of the world's population rely on traditional medicine systems; particularly botanical-based therapies for their primary health care needs [1]. Botanicals have formed the basis of many therapies in traditional systems of medicine such as Ayurveda and Traditional Chinese medicine for thousands of years. The science of Ayurveda, the traditional system of medicine in India, which is more than 5000 years old, includes many botanical-based remedies. Among these is Tinospora cordifolia, known as Amritha in Sanskrit. It recognized as one of the most revered medicinal botanicals in the Ayurvedic Materia Medica because of its prominent healing attributes. The name Amritha is a Hindu mythological term that is described as the heavenly elixir that has saved Devas (benevolent celestial beings) from old age and kept them eternally young. In the epic Bhagavatam written by sage Veda Vyasa, the Devas who exist in Devaloka, a plane similar to that conceived of as Heaven and who were in constant battles with Asuras (malevolent being), sought a remedy to maintain their immortal status when they noticed they were becoming weak and old. When the Devas approached Lord Vishnu, he told them to take Amritha that can be obtained by churning the milky ocean. As the story continued, when the Devas and Asuras recovered the pot of Amritha elixir, they argued about who will serve it. Lord Vishnu appeared in the form of the most beautiful goddess Mohini, who enchanted the Devas and Asuras and agreed to distribute Amritha. According to the epic story, goddess Mohini, deceived the Devas and Asuras by asking them to remain calm with closed eyes until the Amritha is fully served to everyone on the plate in front of them. However, goddess Mohini disappeared with the pot of Amritha elixir into Devaloka and gave it only to Devas allowing them to remain eternally young and immortal. Because of the immortality induced by Amritha, Devas remained undefeated in the battles and thus Asuras were unable to conquer Devaloka. Thus, Amritha came to be known as to impart Immortality.

2. Botanical details

The genus Tinospora (Menispermaceae) includes approximately 32 species of climbing shrubs that are distributed throughout tropical Africa, Madagascar, Australia and the Pacific Islands [2]. The most medicinally and commercially important species , Tinospora cordifolia (Wild.) Miers ex Hook. f. & Thoms., commonly known as Amritha in Sanskrit and South Indian languages or as Guduchi in Hindi is distributed throughout the Indian subcontinent and some adjoining parts of China [3]. The estimated annual consumption Amritha in the Indian System of Medicine is approximately 1,000 tons [4].

Tinospora cordifolia is a glabrous, succulent, climbing shrub. It thrives well in the tropical region and often climbs up the trunks of large trees attaining substantial height. The stem is gray, creamy white and deeply clefted, spirally and longitudinally, with the space in between, spotted with large rosette like lenticels. The wood is white, soft and porous, and the freshly cut surface assumes a yellow tint when exposed to air. Leaves are simple, alternate, exstipulate, long petiolate, chordate in shape showing multicoated reticulate venation. Long thread like aerial roots come up from the branches. Flowers are small and unisexual. Male flowers are in clusters, female flowers are solitary. Six sepals arranged in two whorls, which are obovate and membranous. Aggregate fruit is red, fleshy with many drupelets on thick stalk with subterminal style scars that are scarlet colored [5,6].

3. Traditional use of Amritha in Ayurveda

Amritha is mentioned in various ancient texts of the Ayurvedic system of medicine viz: Sushruta Samhita, Charaka Samhita, Ashtanga Hridaya, Bhava Prakash and Dhanvantari Nighantu [7-11]. In Sushruta Samhita, it is mentioned under Tikta-Saka Varga and described to be useful for treating leprosy, fever, asthma and anorexia [10]. In other treatises like Charaka Samhita and Ashtanga Hridaya, its use against conditions like jaundice, fever and gout is mentioned [9,11]. In Bhavya Prakash, Amritha is described as bitter tonic, astringent, diuretic, aphrodisiac and useful against skin infections, jaundice, diabetes, chronic diarrhea and dysentery [12]. In Dhanvantari Nighantu, its medicinal properties are mentioned for curing bleeding piles, promoting longevity, and curing itching and erysipelas [13]. It is a traditional belief among Ayurvedic practitioners that Amritha extract obtained from the plant growing on Neem tree (Azadirachta indica) is

more bitter and efficacious and is believed to incorporate the medicinal qualities of neem [14].

Amritha is a highly valued medicinal plant in Ayurveda with many roles that are attributed to several medicinally important phytochemicals in different parts of the plant. It is used as a constituent in several folk and Ayurvedic preparations in the form of juice, decoction, paste, powder and pill to treat general debility, fever, skin diseases, chronic diarrhea, jaundice, asthma and bone fracture, which were described in ancient texts. In Ayurveda, different parts of the plant such as leaves, stem, bark, fruits and roots are used for various human ailments. The extracts are reported to possess anti-periodic, anti-spasmodic, anti-microbial, anti-osteoporotic, anti-inflammatory, anti-arthritic, anti-allergic, and anti-diabetic properties [15-17]. Powdered leaves and their decoction are reported to treat gout, ulcers, jaundice, fever, and wounds, and to control blood glucose, along with cow's milk [18]. The extract of stem alone and with honey is useful as a tonic against jaundice, skin diseases [18] and fever [19]; stem extract is also used alone as a tonic. A combination of root and stem is prescribed as an antidote for snake bite and scorpion sting [20]. In North Gujrat (India), root and stem bark of the plant are used along with milk to treat cancer [19]. Fruits are used in the treatment of jaundice and rheumatism [5]. Roots are used as an emetic for visceral obstructions, leprosy, diarrhea and dysentery [5, 21]. It is an active ingredient in Ayurvedic medicines prepared for improving the immune system and the body resistance against infections.

4. Phytochemicals in Amritha

Many of the numerous biologically active compounds, including alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds, and polysaccharides have been isolated from different parts of the plant body [15,16,22]. These compounds are reported to have different biological roles in disease conditions thus enabling potential application in clinical use [15-17,23]. The alkaloids include berberine, bitter gilonin, non-glycoside gilonin gilosterol, etc [5, 22, 23]. Other major phytochemicals in Amritha include tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furano lactone, tinosporidine, columbin, Beta-sitosterol. Berberine, palmatine, tembertarine, magniflorine, choline and tinosporin are contained in the stem of the plant [20,24]. A rearranged cadinane sesquiterpene named tinocordiside, consisting of tricyclic skeleton with a cyclobutane ring, has been isolated from the aqueous fraction of Amritha [25]. Also, the new clerodane furano diterpene 2 with the molecular formula C20H20O8, was isolated from the stem of the plant [26]. Further, a new daucane type sesquiterpene, tinocordifolin, has been isolated from the stem of Amritha along with tinocordifolioside, N-trans-feruloyl tyramine [27]. Phytochemical analysis of the methanol extract of Amritha aerial parts led to the isolation of four new and seven known compounds. The structure of the new aporphine alkaloids are N-formylasimilobine 2-O-β-D-glucopyranosyl –(1-2)-β-D-glucopyranoside (tinoscorside A) , N-acetylasimilobine 2-O- β-D-glucopyranosyl –(1-2)-β-D-glucopyranoside (tinoscorside B), a new clerodane diterpene, tinoscorside C and a new phenylpropanoid, and sinapyl 14-O- β-D-apiofuranosyl-(1-6)-O- β-D-glucopyranoside (tinoscorside D) [28]. The structures and properties of different phytochemicals identified in Amritha have been already compiled in the review articles by Chi et al. [22] as well as Singh and Chaudhari [23].

5.Medicinal Properties

Amritha is used widely in the Ayurvedic system for its general tonic, antiperiodic, anti-spasmodic, anti-inflammatory, antipyretic, anti-arthritic, anti-leprotic, anti-allergic and anti-diabetic properties [29]. Among its common uses are enhancement of immunity and resistance against infections. The root of this plant is reported to have anti-stress and anti-malarial activities. The stem is bitter, stomachic, diuretic, stimulates bile secretions, allays thirst, enriches the blood and cures jaundice. The extract of the stem is also recommended for skin problems. The root and stem of Amritha are used in combination with other drugs as an antidote to snakebite and scorpion [29]. The plant is also used in the treatment of wounds, pneumonia, asthma and cough. It also has anti-cancer, immune stimulating, nerve cell protecting, anti-diabetic, cholesterol-lowering and liver-protective properties. Amritha extract decreases the tissue damage caused by radiation and chemotherapy [30]. Its pharmacological

actions, Amritha target body organs, mainly kidney, liver and spleen [15,24]. Several in vitro and in vivo studies have identified the unique medicinal properties of Amritha extracts (Table 1). Although the entire plant parts of Amritha have been described for various medicinal properties, our research efforts based on ethnobotanical evidence have been focused the immunostimulatory properties against human malignancies and pathogenic infections attributed to stem extracts. The research, starting in early 2000 identified a 550 kDa polysaccharide capable of stimulating immune system. This polysaccharide molecule has (1→4) linked glucopyranosyl units in the main chain with (1→6) linked glucopyranosyl unit branches and a 0.15□of branching. Further, this polysaccharide identified as (1,4)-α-D-glucan (RR1) was non-cytotoxic and did not induce proliferation in normal lymphocytes or tumor cell lines [60]. The α-D-glucan activated different subsets of lymphocytes such as natural killer cells, cytotoxic T lymphocytes, and B cells. The significant activation of NK cells is associated with the dose-dependent killing of tumor cells by activated normal lymphocytes (NK and cytotoxic T lymphocytes) in the functional assay. Immune activation by RR1 elicited the synthesis of pro and anti-inflammatory cytokines leading to a Th1 pathway of T helper cell differentiation. Further, RR1 stimulates the immune system through the Toll-like receptor-6 signaling of NK-kB activation in the macrophages leading to cytokine synthesis [61]. This RR1 activation of innate immunity may serve as a gold standard for testing the immune stimulating properties of other natural products [62-64].

In an endotoxemia rat model, we have shown that treatment of endotoxin-stimulated juvenile rats with 10 mg/kg RR1 differentially modulates cytokine response in the lung and spleen and modifies the pro- and anti-inflammatory balance during an early period of endotoxemia [65,66]. It is possible to prepare RR1 enriched nutraceutical by a proprietary aqueous extraction of stem powder that can be used clinically. However, we developed a propriety stem extract, T2CA, with comparable efficacy for improving immune function and which can be produced in greater abundance (Fig. 1A-E and Table 2). We have shown that T2CA inhibits the migration of human glioblastoma cells in the in vitro scratch assay by down regulating the expression of galectin-3 and matrix metalloproteinase genes (MMP2 and MMP9) [62]. Moreover, T2CA can significantly increase the survival of AKR/J mice injected with ascites tumors. In short, the immune modulatory profile of these compounds may have a role in the prevention and treatment of infection with pandemic viruses such as SARS-COV2, Influenza, etc., and potentially in the prevention of cancers.

6. Safety evaluation of Amritha

Clinical use of Amritha over centuries are in a way themselves evidence of therapeutic utility and safety. No adverse effects have been reported for Amritha with typical treatment regimens. Amritha is advocated as a tonic in infants and children to facilitate growth. The LD50 value for Amritha extract is higher than 1 g/kg for oral administration [67]. Acute toxicity study with the dose of 3 g/kg demonstrated that Amritha does not have any side effects and no reported deaths in rat toxicity studies [68]. When administered in doses of 0.1 g/kg for 12 weeks, Amritha does not trigger any toxic effect on liver and renal function parameters in rats. It precipitated the increment of leukocytosis with neutrophilia in rats while no such effect was observed in healthy humans [69,70]. Amritha extract treatment does not display clastogenicity or DNA damaging effect in bone marrow erythrocytes and peripheral blood lymphocytes [71]. No neurological impairment or marked central nervous system depressant activities were shown [72]. Administration of Amritha to healthy volunteers has been found to be safe in a phase I study, and was well tolerated [67,73]. It has also been shown not to exert any conspicuous adverse reactions on the gastrointestinal system, renal system, cardiovascular system, and central nervous system [74].

7.Conclusion

Limitation of modern therapeutics in sudden outbreaks of pathogens as SARS-CoV-2 have become apparent. Therefore, enhancement of immunity is perhaps the best near-term, broad-based approach available to mitigate the more severe clinical manifestations and mortality of these pandemics until effective therapeutics and vaccines can be developed and distributed worldwide. The role of Amritha for boosting the immune system would be of great use globally in such situations. Realizing the importance

of this fact, Ayurvedic government institutions in India have promoted the use of Amritha and other useful herbal medicines in COVID-19 patients12. Also, the prevention of human malignancies by boosting the immune system with the use of immune stimulating herbs like Amritha is one of the important ways to avoid development of human cancers. Amritha can be used in a variety of forms including powdered nutraceuticals and water-soluble preparations in soft drinks, milk and other food products. Before the nutraceutical is used widely, data needs to be collected to determine an optimal dose, dosing frequency and the duration of immune enhancing effects. Nevertheless, it is noteworthy that in India which has a high population density and where the use of Amritha and many other Ayurveda-based medicinals are very prevalent, the infection and mortality rate from the current COVID-19 pandemic is among the lowest in the world.

8. References

1. World Health Organization. Traditional medicine growing needs and potential. WHO policy perspectives on medicine, No. 2. WHO/EBM/2002. WHO: Geneva; 2002; (WHO, 2003, Revised Traditional Medicine Facts Sheet No 134. http://www.who.int/mediacentre/factsheets/fs134 /en)
2. 2. Udayan PS, Pradeep AK, Balachandran I. A new species of Tinospora (Menispermaceae) from South India. Edinb J. Bot. 2009; 66: 77-80.
3. 3. Chadha YR. The Wealth of India. Publication and Information Directorate, CSIR, New Delhi,
4. 1948; p33.
5. 4. Sharma A, Shanker C, Tyagi LK, Singh M, Rao CV. Herbal Medicine for market potential in India: An Overview. Acad. J Plant Sci. 2008; 1: 26-36.
6. Anonymous. Wealth of India. Raw Materials. Council of Scientific and Industrial Research, New Delhi. 1976; 10: 251-252.
7. 6. Kirtikar KR, Basu BD. Indian Medicinal Plants Vol.2 (Lalit Mohan Basu, Leader Road, Allahabad). 1933; p77.
8. 7. Mitra R, Raghunandan K. Pharmacognosy of Indigenous Drugs Vol. 1; (Central Council for Research in Ayurveda and Siddha, New Delhi). 1982; p321.
9. 8. Sharma PC, Yelne MB, Dennis TJ. Data Base on Medicinal Plants Used in Ayurveda Vol. III, (Documentation & Publication Division, Central Council for Research in Ayurveda & Siddha, New Delhi), 2001; p256.
10. 9. Charaka. Charaka Samhita, Part I & II, (Hindi commentary by Pandey & Chaturvedi), Edited by Rajeshwar Datta Shastri, (Chaukhambha Vidyabhawan, Varanasi) 1961.
11. Sushruta. Sushruta Samhita, commentary by Dalhana, Edited by Jadavji Trikamji Acharya, (Chaukhambha Orientalia, Varanasi & Delhi) 1992.
12. Vaagbhata. Ashtanga hridayam, Commentary by Arunadatta & Hemaadri, collected by Kunt & Narvare and Edited by Paradkara, (Chaukhambha Orientalia, Varanasi & Delhi), 1982.
13. Misra B. Bhava Prakash Nighantu Vol. 1, (Hindi commentary by K C Chunekar), (Chowkhamba Vidya Bhavan, Varanasi), 1969; p269.
14. Aiyer KN, Kolammal M. Pharmacognosy of Ayurvedic Drugs of Kerala. (Central Research Institute Trivandrum) 1963; vol. 6, p28.
15. Watt G. A Dictionary of Economic Products of India, Vol. 6, Reprinted edition (Periodical Experts, Delhi). 1962; p63.
16. 15. Joshi G, Kaur R. Tinospora cordifolia: A phytopathological review. Int. J. Pharmaceut. Sci. Res. 2016; 7: 890-897.
17. 16. Atal CK, Sharma ML, Kaul A, Khajuria A. Immunomodulating agents of plant origin. Preliminary screening. J. Ethnopharmacol. 1986; 18: 133-141.
18. 17. Saha S, Ghosh S. Tinospora cordifolia: One plant, many roles. Anc. Sci. Life. 2012; 31: 151–159.
19. 18. Reddy CS, Reddy KN, Murthy EN, Raju VS. Traditional medicinal plants in Seshachalam hills. J. Med. Plants Res. 2009; 3: 408-412.
20. 19. Bhatt RP, Sabin SD. Contribution to the ethnobotanics of Khedbrahma region of North Gujrat. J. Econ. Taxon. Bot. 1987; 9: 138-145.
21. 20. Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B, Ghose AC. Chemistry and medicinal properties of Tinospora cordifolia (Guduchi). Indian J. Pharmacol. 2003; 35: 83-91.

22. 21. Basha SKM, Umamaheswari P, Rambabu M, Savitramma N. Ethnobotanical study of Mamandur forest (Kadapa-Nallamali range) in Eastern Ghats, Andhra Pradesh. J. Phytol. 2011; 3: 44-47.
23. 22. Chi S, She G, Han D, Wang W, Liu Z, Liu B. Genus Tinospora: Ethnopharmacology, Phytochemistry, and Pharmacology. Evid Based Complement. Altern. Med. 2016;, doi: 10.1155/2016/9232593.
24. 23. Singh D, Chaudhuri PK. Chemistry and Pharmacology of Tinospora cordifolia. Nat. Prod. Commun. 2017; 12: 299-308.
25. 24. Qudrat-I-Khuda M, Khaleque A, Ray NS. Tinospora cordifolia. I. Constituents of the plant fresh from the field. Scientific Res. (Dacca) 1964; 1: 177-183.
26. Ghosal S., Vishwakarma RA. Tinocordiside: a new rearranged cadinane sesquiterpene glycoside from Tinospora cordifolia. J. Nat. Prod. 1977; 60: 839-841.
27. Hanuman JH, Bhat R, Sabata B. A clerodane furano-diterpene from Tinospora cordifolia. J. Nat. Prod. 1988; 51: 197-201.
28. Maurya R, Sukhdev S. Tinocordifolin: A sesquiterpene from Tinospora cordifolia. Phytochemistry 1998; 49: 1343-1345.
29. Kiem PV, Minh CV, Dat NT, Kinh LV, Hang DT, Nam NH, Cuong NX, Huong HT, Lau DT. Aporphine alkaloids, clerodane diterpenes, and other constituents from Tinospora cordifolia. Fitoterapia 2010; 81: 485-489.
30. Joshi V, Joshi RP. Some plants used in Ayurvedic and Homoeopathic Medicine. J. Pharmacogn. Phytochem. 2013; 2: 269-275
31. Pandey M, Vyas MK, Sharma R. Tinospora cordifolia: A climbing shrub in health care management. Int. J. Pharma. Biol. Sci. 2012; 3: 612-618
32. Xavier TF, Anand SP. Antibacterial activity of stem extracts of Tinospora cordifolia. Anc. Sci. Life 2003; 23: 40-43
33. Badar VA, Thawani VR, Wakode PT. Efficacy of Tinospora cordifolia in allergic rhinitis. J. Ethnopharmacol. 2005; 96: 445-459
34. Mishra R, G Kaur. Tinospora cordifolia induces differentiation & senescence pathways in neuroblastoma cells. Mol. Neurobiol. 2015; 52: 719-733
35. Ashok BK, Ravishankar B, Bhat SD. Antipyretic activity of Guduchi ghrita formulations in albino rats. Ayu 2010; 31: 367-370.
36. Kaur M, Singh A, Kumar B. Comparative antidiarrheal and antiulcer effect of aqueous and ethanolic extracts of Tinospora cordifolia in rats. Int. J. Pharmaceut. Tech. Res. 2014; 5: 122-128.
37. Goel B, Pathak N. Clinical evaluation of analgesic activity of Guduchi, Tinospora cordifolia using animal model. J. Clin. Diagn. Res. 2014; 8: 1-4.
38. Wani JA, Neema RK. Phytochemical screening & aphrodisiac activity of Tinospora cordifolia. Int. J. Pharmaceut. Clin. Res. 2011; 3: 21-26.
39. Kumar V, Mahdi F, Chander R, Hussain I. Tinospora cordifolia regulates lipid metabolism in alloxan induced diabetes in rats. Int. J. Pharm. Life Sci. 2013; 4: 3010-3017.
40. Ramesh V, Jayaprakash R, Sridhar MP. Antioxidant activity of ethanol extract of Tinospora cordifolia on N-nitrosodiethylamine induced liver cancer in male wistar albino rats. J. Pharm. Bioallied Sci. 2015; 1: 45-50.
41. Patgiri B, Umretia BL, Prajapati PK, Shukla VJ. Anti-inflammatory activity of aqueous extract of Tinospora cordifolia. Ayurveda 2014; 35: 108-110
42. Ratnasamy R, Compos AM. A new antifeedant clerodane diterpenoid from Tinospora cordifolia. Nat. Prod. Rev. 2013; 27:1431-1436.
43. Gupta R, Sharma V. Ameliorative effect of Tinospora cordifolia root extract on histopathological & biochemical changes induced by aflatoxin b1 in mice kidney. Toxicol. Int. 2011; 18: 94-98.
44. Jain BN, Jain VK, Shete A. Antipsychotic activity of ethanolic extract of Tinospora cordifolia in amphetamine challenged mice model. J. Adv. Pharm. Technol. Res. 2010; 1: 30-33.
45. Dhingra D, Goyal PK. Evidence for the involvement of monoaminergic and GABAergic systems in antidepressant-like activity of Tinospora cordifolia in mice. Indian J. Pharmaceut. Sci. 2008; 70: 761-767.
46. Kapoor P, Jarry H, Wuttke W. Evaluation of antiosteopotential of Tinospora cordifolia in female rats. Maturitas 2008; 59: 329-338.

47. Jagetia GC, Rao SK. Evaluation of antineoplastic activity of Guduchi, Tinospora cordifolia in Ehrlich ascites carcinoma bearing mice. Biol. Pharm. Bull. 2006; 29: 460-466.
48. Gupta RS, Sharma A. Antifertility effect of Tinospora cordifolia stem extract in male rats. Indian J. Exp. Biol. 2003; 41: 8859-8864.
49. Tiwari M, Kakkar P, Dwivedi UN. Tinospora cordifolia extract modulates COX-2, iNOS, ICAM 1, pro-inflammatory cytokines & redox status in murine model of asthma. J. Ethnopharmacol. 2014; 28: 326-337.
50. Mishra R, Kaur G. (2013) Aqueous ethanolic extract of Tinospora cordifolia as a potential candidate for differentiation-based therapy of glioblastomas. PLOS One. 2013; 8: e78764.
51. Singh V, Banyal HS. Antimalarial effect of Tinospora cordifolia and Cissampelos pareira on Plasmodium berghei. Curr. Sci. 2011; 110: 1356-1368.
52. Sharma AK, Kishore K, Sharma D, Agarwal SS, Singh SK. Cardioprotective activity of alcoholic extract of Tinospora cordifolia in CaCl2 induced cardiac arrhythmia in rats. J. Biomed. Res. 2011; 25: 280-286.
53. Nadig PD, Dethe SM, Revankar RR, Aliyar MA. Effect of Tinospora cordifolia on experimental diabetic neuropathy. Indian J. Pharmacol. 2012; 44: 580-583.
54. Antonisamy P, Dhanasekaran M, Balthazar JD. Gastroprotective effect of epoxy clerodane diterpene isolated from Tinospora cordifolia on indomethacin induced gastric ulcers in rats. Phytomedicine 2014; 21: 966-969.
55. Stance MH, A Nagy A, Tosa M, Vlad L. Hepatoprotective effect of orally administered melatonin and Tinospora cordifolia in experimental jaundice. Chirurgia (bucur). 2011; 106: 205-210.
56. Patel MB, Mishra S. Hypoglycaemic activity of alkaloidal fraction of Tinospora cordifolia. Phytomedicine 2011; 18: 1045-1052.
57. Gupta MS, Sharma GD, Chakraborty BE. Effect of aqueous extract of Tinospora cordifolia on functions of peritoneal macrophages isolated from CCl4 intoxicated male albino mice. BMC Complement. Altern. Med. 2011; 11: 102-111.
58. Gupta A, Raj H, Upmanyu N. Evaluation of Bacopa monnieri, Evolvulus alsinoides, Tinospora cordifolia and their combinations on cognitive functions in rats. Curr. Aging Sci. 2013; 6:239-243.
59. Kosaraju J, Roy PD. Neuroprotective effect of Tinospora cordifolia ethanol extract on 6-hydroxydopamine induced Parkinson disease. Int. J. Pharmacol. 2014; 46: 176-180.
60. Patel A, Singh CS, Patel NS. Radioprotective & cytoprotective activity of Tinospora cordifolia stem enriched extract containing cordifolioside. Indian J. Pharmacol. 2013; 45: 237-243.
61. Nair PKR, Rodriguez S, Ramachandran R, Alamo A, Melnick SJ, Escalon E, Garcia Jr PI, Wnuk, SF, Ramachandran C. Immune stimulating properties of a novel polysaccharide from Tinospora cordifolia. Int. Immunopharmacol. 2004; 4: 1645-1659.
62. Nair PKR, Melnick SJ, Ramachandran R, Escalon E, Ramachandran C. Mechanism of macrophage activation by (1,4)-α-D-glucan isolated from Tinospora cordifolia. Int. Immunopharmacol. 2006; 6: 1815-1824.
63. Ramachandran C, Quirin K-W, Escalon E , Melnick SJ. Immune stimulating and galectin-3 inhibitory effects of a hydrophilic polysaccharide nutraceutical from Tinospora cordifolia. Int. J. Phytomed. 2020, 12 (http://dx.doi.org/10.5138/09750185.2449).
64. Ramachandran C, Wilk BJ, Hotchkiss A, Chau H, Eliaz I, Melnick SJ. Activation of human T-helper/Inducer cell, T-cytotoxic cell, B-cell, and natural killer (NK) cells and induction of natural killer cell activity against K562 chronic myeloid leukemia cells with modified citrus pectin. BMC Complement. Altern. Med. 2011; 11: 59-68.
65. Rachmut I, Samuels N, Melnick SJ, Ramachandran C, Sharabi Y, Pavlovsky A, Maimon Y, Shoham J. Immunomodulatory effects of the botanical compound LCS101: implications for cancer treatment. OncoTargets Ther. 2013; 6: 1-9.
66. Velazquez EA, Kimura D, Torbati D, Ramachandran C, Totapally BR. Immunological response to (1,4)-α-D-glucan in the lung and spleen of endotoxin-stimulated juvenile rats.

Basic Clin. Pharmacol. Toxicol. 2009; 105: 301-306.
67. Koppada R, Norozian FM, Torbati D, Kalomiris S, Ramachandran C , Totapally BR. Physiological effects of a novel immune stimulator drug, (1,4)-α-D-glucan, in rats. Basic Clin. Pharmacol. Toxicol. 2009; 105: 217-221.
68. Rege NN, Thatte UM, Dahanukar SA. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. Phytother. Res. 1999; 13 : 275-291.
69. Agarwal A, Malini S, Bairy KL, Rao MS. Effect of Tinospora cordifolia on learning and memory in normal and memory deficit rats. Indian J. Pharmacol. 2002, 34: 339-349.
70. Panchabhai TS, Kulkarni UP, Rege NN. Validation of therapeutic claims of Tinospora cordifolia: a review. Phytother. Res. 2008; 22: 425.441.
71. Manjrekar PN, Jolly CI and Narayanan S. Comparative studies of the immunomodulatory activity of Tinospora cordifolia and Tinospora sinensis. Fitoterapia. 2000, 71: 254– 257.
72. Chandrasekaran CV, Mathuram LN, Daivasigamani P, Bhatnagar U. Tinospora cordifolia, a safety evaluation. Toxicol. In Vitro. 2009; 23: 1220–1226.
73. Karkal YR and Bairy LK. Safety of aqueous extract of Tinospora cordifolia (Tc) in healthy volunteers: a double-blind randomized placebo-controlled study. Iranian J. Pharmacol. Ther. 2009; 6: 59–61.
74. Nayampalli SS, Ainapure SS, Samant BD, Kudtarkar RG, Desai NK and Gupta KC. A comparative study of diuretic effects of Tinospora cordifolia and hydrochlorothiazide in rats and a preliminary phase I study in human volunteers. J. Postgrad. Med. 1988; 34: 233–236.
75. Upadhyay AK, Kumar K, Kumar A, Mishra HS. Tinospora cordifolia (Willd.) Hook. f. and Thoms. (Guduchi)— validation of the Ayurvedic pharmacology through experimental and clinical studies. Int. J. Ayurveda Res. 2010; 1: 112–121.

Figure 1: (**A**) *Tinospora cordifolia* climber with heart shaped leaves and red colored fruits (**B**) Dried stem to prepare the nutraceutical (**C**) Water soluble immune stimulating nutraceutical powder prepared from the dried stem (**D**) Capsules (100 mg) (**E**) Enteric coated tablets (50 mg).

Table 1: Medicinal properties of Amritha extracts

Activity	Plant part/Extract	Investigated animal model/cell line
Antibacterial activity	Stem/Aqueous and ethanolic extract	Microorganisms used: *Escherichia coli, Proteus vulgaris, Enterococcus faecalis, Salmonella typhi, Staphylococcus aureus and Serratia marcescens* [31]
Allergic rhinitis	Aqueous extract	Double blind placebo control trial [32]
Anticancer activity	Aqueous and ethanolic extract	IMR32 human neuroblastoma cell lines as a model [33]
Antipyretic activity	Formulation of Guduchi ghrita	Albino rats against yeast induced pyrexia [34]
Antidiarrheal activity	Whole plant/Ethanolic extract	Castor oil and magnesium sulfate induced diarrhea [35]
Antiulcer activity	Aerial parts/Ethanolic extract	Albino rats using pylorus ligation induced ulcer [35]
Analgesic activity	Whole plant/Aqueous extract	Hot plate and abdominal writhing method of albino rats [36]
Aphrodisiac activity	Aqueous and hydroethanolic extract	Adult albino rats of Wistar strain [37]
Antidyslipidemic activity	Stem/Aqueous extract	Alloxan induced diabetic male adult rats of Charles Foster strain [38]
Antioxidant activity	Whole plant/Ethanolic extract	n-nitrosoethylamine induced liver cancer in male Wistar albino rats [39]
Anti-inflammatory activity	Stem/Aqueous extract	Carrageenan induced paw edema model in rats [40]
Antifeedant activity	Whole plant/Chloroform extract	Microorganisms used: *Earias vitella, Plutella zylostella, Spodoptera litura* [41]
Ameliorative effect on toxin	Root/Ethanolic extract	Male Swiss albino mice exposed to aflatoxin [42]
Antipsychotic activity	Aqueous and ethanolic extract	Amphetamine challenged mice model [43]
Antidepressant activity	Ether extract	Swiss albino mice and activity evaluated by tail suspension test and forced swim test [44]
	Stem/ethanolic extract	Female Sprague-Dawley rats [45]

Antiosteoporotic activity		
Antineoplastic activity	Aerial parts/ Dichloromethane extract	Mice transplanted with Ehrlich ascites carcinoma [46]
Antifertility effect	Stem/Methanolic extract	Male rats [47]
Antiasthmatic activity	Stem/hydroethanolic extract	In vivo asthma model: Mice were sensitized with intraperitoneal ovalbumin followed by intranasal ovalbumin treatment [48]
Antitumor activity	Aqueous and ethanolic extract	Cell proliferation decreased in C6 glioma cells in dose-dependent manner [49]
Antimalarial activity	Stem/Ethanolic extract	Microorganism used: *Plasmodium berghei* on white swiss mice [50]
Cardioprotective effect	Whole plant/Ethanolic extract	Calcium chloride administered by intravenous infusion to produce arrhythmia in rats [51]
Diabetic neuropathy	Stem/Aqueous extract	In vitro aldose reductase inhibition assay and Streptozotocin induced Wistar albino diabetic rats; in vivo results analyzed by Mann Whitney Test [52]
Gastroprotective effect	Whole plant	Indomethacin indued gastric ulcer in rats [53]
Hepatoprotective effect	Whole plant/Aqueous extract	Bile duct ligation induced jaundice in rats [54]
Hypoglycemic effect	Stem/Aqueous extract	Induce insulin in rat pancreatic β-cell lines [55]
Immunomodulat-ory activity	Whole plant/Aqueous extract	Swiss model albino mice [56]
Nootropic effect	Whole plant/Ethanolic extract	Amnesic rats using radial arm maze task performance and Barnes maze test [57]
Neuroprotective effect	Aerial parts/Ethanolic extract	6-hydoxy dopamine lesion rat models of Parkinson's disease [58]
Radioprotective and cytoprotective effect	Stem/Ethanolic extract	4Gy-γ-radiation in albino mice and cyclophosphamide induced genotoxicity [59]

Table 2: Monosaccharide composition of immune stimulating nutraceutical (T2CA) extract from Amritha stem*

Monosaccharide	Mole (%)
Arabinose	8.9
Rhamnose	4.4
Fructose	0.4
Xylose	2.8
Unidentified peak	15.8
Glucuronic acid	0
Galactouronic acid	13.9
Mannose	2.7
Galactose	9.1
Glucose	32.9
N-Acetyl Galactosamine	0
N-Acetyl Glucosamine	0
N-Acetyl Mannosamine	0

*Glucosyl composition analysis by GC-MS [62]