सत्यमेव जयते

Government of India

Ministry of Ayush

Technical Dossier on Guduchi

(Tinospora cordifolia)

Guduchi is a herb that has been used extensively throughout history from ancient times to modern days with encouraging medicinal value and tremendous potential in terms of health benefits. This dossier is a comprehensive review of literature related to Guduchi and its benefits for the promotion of health.

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Guduchi

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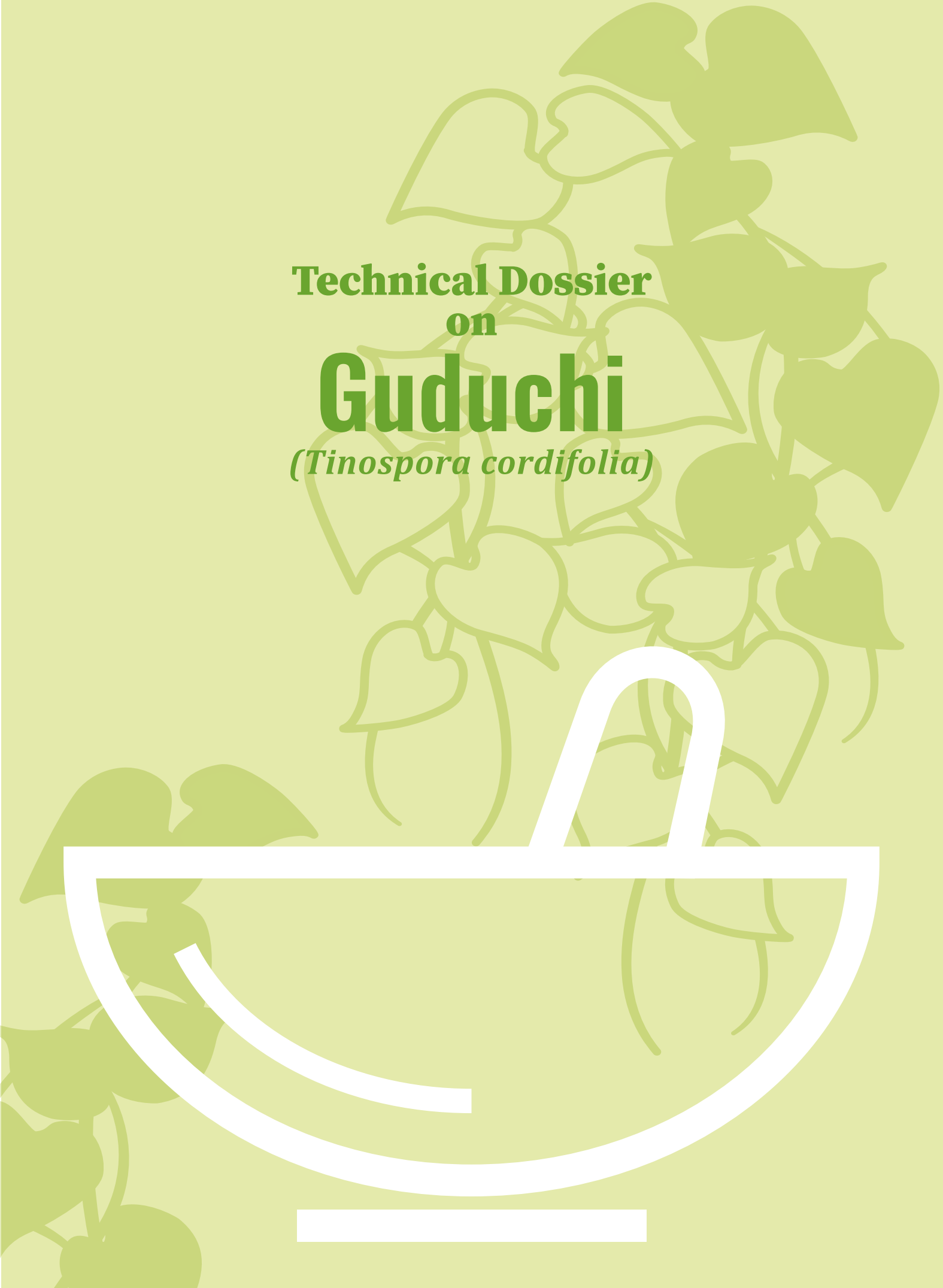

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General Disclaimer:

The content of this book is for informational purposes only and does not substitute professional medical advice or consultation with healthcare professionals.

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SCOPE OF WORK

The Terms of References (TOR) for the committee to prepare a technical dossier on the safety study of Guduchi were included the below:

1. Description of Guduchi in authoritative literature for ASU drugs as mentioned in the First Schedule of Drugs and Cosmetics Act, 1940
2. Description of Guduchi plant, parts used, and its important formulations along with their indications as per authoritative literature for ASU drugs / Ayurvedic Pharmacopoeia of India / Ayurvedic Formulary of India.
3. Description regarding Safety and pharmacological properties of Guduchi.
4. Relevant references and outcomes of research studies conducted on Guduchi.
5. Any other information related to Guduchi may be useful for its propagation/ creating awareness among the general public.

COMMITTEE

(That Prepared the Technical Dossier on Guduchi
File No. L-11011/9/2021-DCC-Part(1) dated 21.02.2022)

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PROLOGUE

On behalf of all the members of the committee constituted by the Ministry of AYUSH, Government of India for the preparation of a technical dossier on *Guduchi*, I wish to sincerely thank the Ministry of Ayush, the Honourable AYUSH Minister, GOI, and the Secretary of the Ministry of Ayush, GOI for nominating us to this committee. I wish to express my gratitude for enabling us to prepare this dossier that has led to this important work that could benefit and impact the health of the population in the entire country and worldwide, thereby leading to improving the health of mankind.

Guduchi is an herb that has been used extensively throughout history from ancient times to modern days with encouraging medicinal value and tremendous potential in terms of health benefits. However, recently few publications have created panic in the mind of the general public and practitioners of Ayurveda by raising safety concerns about the liver toxicity potential of *Guduchi*. This dossier is a comprehensive review of literature related to *Guduchi* and stands to allay the safety concerns raised and to list the overall benefits of *Guduchi* for the promotion of health.

This dossier has been made possible with the help and support of many academics, clinicians, and researchers of AYUSH without whom such a comprehensive work would not have been possible in such a short time. I am personally appreciative of the tireless work undertaken by Dr. Galib and his team who coordinated with the members of the task force. I also want to put my personal thankfulness to Dr. Bhavana Prasher and Prof. R.K. Garg and their respective teams of contributors. I am grateful to Dr. Anand T. Gudivada, Dr. N. Srikanth, and Prof. Dr. G.G. Gangadharan for their useful, timely, and crucial contributions and guidance without which this document may not have seen the light of the day. I also would like to acknowledge the support extended by Prof Rabi Narayan Acharya, Director General, CCRAS. Many contributors have aided directly or indirectly in the process of preparation of this dossier. I am personally grateful to all of them. All of these people are extremely busy in their respective endeavors and fields of activities, and it is their commitment to the cause of health in general and Ayurveda, in particular, that they have been able to spare valuable time from their hectic schedules. We are short of the appropriate vocabulary to express our appreciation to all of them and their team members. Inadvertently, some names may have been missed out on the list of contributors for which I personally take all responsibility and sincerely express my apology.

On behalf of the committee, I reiterate that we are grateful for this opportunity and hope that this dossier is a useful contribution to the health promotion of the population at large. We are optimistic that this technical dossier will help to rekindle the interest in *Guduchi* to serve the health needs of society. We also hope that this comprehensive document will be able to dispel all the unfounded fears about this celebrated herb which has been used by humankind all over the world from ancient to modern times.

Prof. MLB Bhatt
Former Vice Chancellor
King George's Medical University,
Lucknow and Chairperson,
Committee for Technical Dossier
on Guduchi

BACKGROUND

Traditional medicines form an important part of global healthcare. It is estimated that 80% of the world's population living in the developing world rely on herbal medicinal products as a primary source of healthcare and traditional medical practice, as an integral part of the culture in those communities.[1] These are often used to provide first-line of care and basic health services to people living in remote and poor areas. Even in areas where modern medicine is available, the interest in herbal medicines has been increasing rapidly in recent years. The significant contribution made by herbal medicines to human health has led to increased official and commercial interest. The contribution of Ayurveda through its herbal remedies in global health care cannot be ignored by any science for its qualitative strength and benefits provided in the field of therapeutics. The long history of their usage in different pathological manifestations is a proof of their safe, efficacious and beneficial effects. These formulations gained tremendous popularity during the COVID-19 pandemic. The World Health Organization (WHO) also welcomed innovations around the world including repurposing of drugs, and traditional medicines and developing new therapies in the search for potential treatments for COVID-19.[2]

When the planet confronted the COVID 19 in 2020 as a global pandemic,[3] modern medicine had not much to offer for the prevention or treatment. Everyone was groping in the dark with new hypotheses, which were propounded every day for new treatment protocols being recommended with a claim to be effective against this dreaded disease. The Ministry of Ayush is committed to helping the nation with the large resource of time-tested traditional knowledge practiced in this continent for the benefit of mankind. Ayurveda, being rooted in the philosophy of *Swasthasya swasthya rakshanam, aaturasya vikara prashamanam* (to help the healthy person to protect and maintain his wellness and to help a diseased person to become healthy), focused on developing treatment strategies to address the pandemic situation using available drugs from AYUSH armamentarium.

Tinospora cordifolia, commonly known as *Guduchi or Giloy,* familiar as *Amrita* in Sanskrit, which literally translates to the 'herb of immortality', because of its abundant beneficial properties. It has a popular and an important place in the therapeutic armamentarium of traditional ayurvedic medicine, both for preventive and promotive health as well as curative medicine. It is used for ages in the treatment of various diseases including fever, jaundice, chronic diarrhea, skin diseases, eye disorders, metabolic and joint disorders etc. It is attributed with the properties of immune-modulation and rejuvenation. Recently, the discovery of active components from this plant

and their biological functions in disease control has led to active interest in this plant across the globe.

Tinospora cordifolia is immensely useful due to the presence of different compounds of pharmaceutical significance belonging to various groups such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, and phenolics. These compounds possess pharmacological properties, which make it anti-diabetic, antipyretic, anti-inflammatory, anti-oxidant, hepato-protective, and immuno-modulatory.[4] Further, the herb has been attributed with Anti-toxic, Anti-infective, Anti-arthritic, Anti-osteoporotic, Anti-diabetic, Anti-HIV, Anti-microbial, Anti-oxidant, etc. activities.[5] Its secondary metabolites are reported to inhibit the SARS-CoV-2 main protease with high binding efficiency and these metabolites can help as an antidote for SARS-CoV-2.[6] This new knowledge about the usage of *T. cordifolia* led to its widespread use during the COVID-19 pandemic.

Besides the growing demand and acceptance for traditional medicine, few concerns surfaced in the recent past about their usage. This happened in the case of *Tinospora* too. It has been known that 34 species of *Tinospora* are available in various geographical regions of the world. Many of them have been investigated for their medicinal value. *T. cordifolia* is well recognized and discussed in classical texts of Ayurveda, and the official texts of the Drugs and Cosmetics Act 1940 also recommended the use of *T. cordifolia* in therapeutics as a safe and efficacious herb in different dosage forms. While certain other species are reported to cause hepatotoxicity. Thus, proper identification and appropriate use of this herb become an essential aspect of safe practice. The current dossier is an attempt to showcase and discuss the therapeutic potential and clarify safety issues of *Tinospora cordifolia*.

Giloy
Amrita
Tinospora Cordifolia
Guduchi

GUDUCHI - CLASSICAL CONTRIVE & QUALITY PROFILES

Introduction:

Guduchi (*Tinospora cordifolia* (Willd.) Hook. f. and Thoms.) is a large, deciduous climbing shrub belonging to the family Menispermaceae. It is distributed throughout the tropical Indian subcontinent. Across the country, the plant is commonly known as Giloy. In Ayurveda, it is said to be one of the best *Rasayana* (Rejuvenator). A special focus has been made on its health benefits in treating various disorders and its potential as an immune booster and aiding in the betterment of human life expectancy. It is also popular in Ayurveda medicine for its immense therapeutic applications. Enormous information on the utility of the herb in the management of various diseases is described vividly in classical literature.

Description of actions and indications of *Guduchi* in different texts through different time frames confirm the continued use of the drug since long time. New actions such as *Balya* (~Strength promoting), *Chakshusya* (~beneficial for eye health) and its use in *Visarpa* (~Spreading cellulitis/ Erysipelas), *Pandu* (~Anemia), *Krimi* (~Worm infestation), *Arati* (~Distress), *Bhrama* (~Dizziness), and *Kasa* (~Cough) were reported during later period.[7] Charaka samhita has considered *Tinospora* among four *Medhya rasayana* (~Intellect enhancer) drugs. Individually or in combination with other drugs, *Tinospora* is considered as an important drug by other scholars also in the management of *Vatarakta* (~Gout), *Kushtha* (~Various skin diseases), *Jvara* (~Fever), *Kamala* (~Jaundice), and *Prameha* (~Excessive urination) etc.[8]

About 2400 Ayurveda formulations contain *Guduchi* as an ingredient. These formulations, are made in more than 24 dosage forms like *Kwatha* (~Decoction), *Hima* (~Cold infusion), *Churna* (~Powder), *Swarasa* (~Juice), *Kalka* (~Paste), *Gutika* (~Tablet/Pill), *Ghrita* (~Medicated Ghee), *Avaleha* (~Semisolid medicated confection), *Taila* (~Medicinal oil), *Guggulu* (~Medicinal Resin), *Asava* (~Fermented infusion), *Arishta* (~Fermented decoction), *Arka* (~Liquid preparation obtained by distillation), *Modaka* (~Formulated pill), *Yavagu* (~Medicated gruel), *Bhasma* (~Ashes of metals), *Kshara* (~Alkalies), *Satva* (~Essence), *Vataka* (~Pill), *Kshirapaka* (~Medicated milk), *Sneha* (~Lubricant), *Takra* (~Buttermilk), *Yusha* (~Soup) *and jala* (~Water), are indicated for treatment in about 95 clinical conditions. About 141 formulations in 14 various dosage forms for topical application contain *Guduchi* as an ingredient that are indicated in 65 disease conditions.[8] Its versatile use in multiple clinical conditions and in various dosage forms, through multiple routes of administration (oral, topical, nasal, per-rectal etc) justifies one of its synonym *Bhishagpriya* (~favored by physicians) (Annexure 1).

This herb is also being used as traditional medicine by indigenous groups throughout the tropical and subtropical parts of Asia, Africa, and Australia.[9]

The extensive literature survey revealed that *Tinospora* has a widespread distribution, targeted clinical application, and diverse biological and pharmacological activities. This has also triggered a lot of interest amongst modern scientists who have carried out extensive studies on Guduchi. Phytochemical researches revealed the extensive presence of terpenoids, alkaloids, polysaccharides, and other compounds. The extensive literature survey revealed *Tinospora* species to be a group of important medicinal plants used for the ethnomedical treatment of cold, headache, pharyngitis, fever, diarrhea, oral ulcer, diabetes, digestive disorder, and rheumatoid arthritis. Indian ethnopharmacological data points to the therapeutic potential of the *T. cordifolia* for the treatment of diabetic conditions. The medicinal applications of *T. cordifolia* in countering various disorders and usages as anti-oxidant, anti-hyperglycemic, anti-hyperlipidemic, hepatoprotective, neuroprotective, osteoprotective, radio-protective, anti-anxiety, adaptogenic, analgesic, anti-inflammatory, antipyretic, a thrombolytic agent, anti-diarrheal, anti-ulcer, anti-microbial and anti-cancer agent have also been established.

Botanical name and family:

The botanical name of Guduchi / Giloy is *Tinospora cordifolia* (Willd.) Hook.f. & Thomson belonging to the family Menispermaceae.[10] It consists of dried pieces of the mature stem.

Distribution:

A perennial climber found throughout tropical India, ascending to an altitude of 900 m from Kumaon eastward as well as southwards upto Shri Lanka. It is usually collected during summer preferably in the month of May.[11]

Habit:

Climber

CHRONOLOGICAL REVIEW

Vedic period:

Its antecedence dates back to very early times in Indian Medicine. It has been advocated to keep it in every house to avoid and control entry of microorganisms.

Samhita & Nighantu period:

It is one of the non-controversial and extensively used herbs in Ayurvedic medicine. *Brihattrayi* (the three major classical texts) mentioned the herb at several times with important therapeutic applications. Charaka quoted it among the *Agrya dravyas* (principal drugs).[12] He also identified it as one of the best Medhya *Rasayanas* (~brain tonics). By the period of Nighantu, the descriptions of Guduchi in therapeutics have been increased to manifolds.

CATEGORIZATION IN CLASSICAL LITERATURE:

Guduchi has been widely recognized in almost all classical texts and has been included in various groups of plants based on its pharmacological action. Details of this information is as below:

1	*Charaka Samhita*	Vayahsthapana (~Prolonging youth), Daha prashamana (~Relieving burning sensation), Trishna nigrahana (~Anti-dypsic), Triptighna (~Anti-satiative), Stanyashodhana (~Galacto-depurant), Sandhaniya (~Tissue binding), Snehopaga (~Oleating)
2	*Sushruta Samhita*	*Guduchyadi, Patoladi, Valli Panchamula, Kakolyadi, Aragvadhadi*
3	*Ashtanga Samgraha*	*Guduchyadi, Patoladi, Aragvadhadi*
4	*Dhanvantari Nighantu*	*Guduchyadi varga*
5	*Shodhal Nighantu*	*Guduchyadi varga*
6	*Madhava Dravyaguna*	*Shaka varga*
7	*Madanpala Nighantu*	*Abhayadi varga*
8	*Raja Nighantu*	*Guduchyadi varga*
9	*Kaiyadev Nighantu*	*Aushadhi varga, Chaturbhadra (Mishraka Varga)*
10	*Bhavaprakasha Nighantu*	*Guduchyadi varga*
11	*Saraswati Nighantu*	*Latadi varga*
12	*Shaligrama Nighantu*	*Guduchyadi varga*
13	*Haritakyadi Nighantu*	*Shaka varga*
14	*Priya Nighantu*	*Pippalyadi varga*

Further, *Guduchi* has been mentioned in 68 groups/ sections based upon its origin, morphology, properties, pharmacodynamics, therapeutic use, habit, action on *dosha* (~regulatory functional factors of the body) and disease conditions etc.

S. No.	Basis of classification/ Nomenclature of class	Categorized under
1	Based on Habit	*Valli kanda, Valli Panchamula, Vrikshadi varga, Lata varga, Lata kanda*
2	Based on action	*Daha prashamana mahakashaya (~group of ten drugs that alleviate burning sensation), Dahaghna (~reduces burning sensation), Jvaraghna (~anti-pyretic), Sandhaniya (~tissue binding), Stanya Shodhana (~Galacto-depurant), Snehopaga (~oleation assisting) Triptighna (~anti-satiative), Trishnaghna (~anti-dypsic), Vayahsthapana Gana (~prolonging younger age), Jvarahara (~anti-pyretic), Prajasthapana (~sustenance of fetus).*
3	Based on properties	*Katu skanda (~drugs having action attributed to pungent taste), Madhura skanda (~drugs having action attributed to sweet taste), Tikta varga, Tikta skanda (~drugs having action attributed to bitter taste)*
4	Based on the name of first drug in the group	*Aragvadhadi Gana, Gokshuradi Gana, Guduchyadi Gana, Kakolyadi Gana, Kiratadi Gana, Murvadi Gana, Mustakadi Gana, Padmakadi Gana, Patoladi Gana, Rasnadi Gana, Shatarvaryadi Gana, Shatayadi Varga, Shyamadi Gana, Triphaladi Gana, Vidarikandadi Gana, Brihat Shatayadi Varga, Bilvadi Varga, Pippalyadi Varga, Abhayadi Varga, Madanadi Varga*
5	Based on the Number of plants in the group	*Panchadasha Gana, Chatushpada Varga*
6	Based on *Dosha Karma*	*Kapha Samshamana (~pacifies kapha) varga, Vata Samshamana (~pacifies vata) varga, Tridoshaghna (~pacifies all the vitiated doshas) dravya, Kaphavataghna (~pacifies kapha and vata) varga*
7	Based on use	*Aushadhi varga*
8	Others	*Chaturbhadra Varga, Maraka Varga, Panchatiktam Varga, Shamana Dravya, Aushadha ashraya parichchheda, Panchamrita yoga, Trayantikadi Gana, Dvittiyakanda Vanaushadhi varga, Shaka varga*

Synonyms:

More than 75 synonyms have been referred for *Tinospora* in Ayurvedic literature inferring its importance in therapeutics. A few to refer to are:

S.No	SYNONYMS	PROBABLE MEANING
	Based on Propagation	
1	*Bahuchhinna, Chhinna, Chhinnanga, Chhinnarohaka, Chhinnaruha, Chhinnodbhava*	Grows from the point from where it is sliced
2	*Amara, Amrita, Amritahvaya, Amrita lata, Amrita valli, Amritavallari*	A climber that never dies. Even a sliced piece of stem is sufficient for propagation
3	*Kaandajata, Kaandodbhava*	Propagated through stem
	Based on Pharmacognostical character	
4	*Kundali, Mandali*	Ascending on the host in a circular way
5	*Naga kumari, Naga kanyaka*	The stem has a twining nature comparable to that of young snakes
6	*Tantri / Tantrika*	The stem appeared like a spiral rope
7	*Chakra lakshanika, Chakra lakshana, Chakra lakshani, Chakrangi*	The transverse section of the stem shows a circular structure
8	*Madhuparni*	Leaves have viscid juice like honey
9	*Chandrahasa*	The seeds are semilunar shaped
	Based on Pharmacological action	
10	*Jvaranashini, Jvarari*	Pacifies pyrexial conditions
11	*Jivanti, Rasayani, Vayahstha, Vayasya*	Owing to its Rasayana (rejuvenating) properties
12	*Guduchika, Guluchi*	It provides protection against many diseases
13	*Soma, Soma valli*	It promotes strength and vitality
14	*Vishaghni, Vishapa*	Helpful in poisonous conditions
15	*Vranaha*	Helpful in wound healing
16	*Vataraktari*	Alleviates Vatarakta
	Based on Mythological background	
17	*Deva Nirmita, Devi, Amrita sambhava, Surakrita*	Originated from the nectar drops showered by Lord Indra

S.No	SYNONYMS	PROBABLE MEANING
	Others	
18	*Vatsadani*	The calves will eat this plant
19	*Bhishakapriya, Bhishakajita*	Preferred herb of many physicians
20	*Vara*	The best among various medicines

All such synonyms infer that the plant has multidimensional healing potency, and it protects individuals from various diseases.

Vernacular Names:[13]

Assamese	-	**Siddhilata, Amarlata**
Bengali	-	**Gulancha**
Gujarati	-	**Galac, Garo**
Hindi	-	**Giloy, Gurcha**
Kannada	-	**Amrutaballi**
Kashmiri	-	**Amrita, Gilo**
Malayalam	-	**Chittamrutu**
Marathi	-	**Gulvel**
Oriya	-	**Guluchi**
Punjabi	-	**Gilo**
Tamil	-	**Seendal, Seendil kodi**
Telugu	-	**Thippateega**
Urdu	-	**Gilo**

Names in different Indian Systems of Medicine (ISM)

- Ayurveda - **Guduchi**
- Siddha - **Cintil Tantu**
- Unani - **Gilo**

PROPERTIES & ACTIONS:

Rasa	Guna	Virya	Vipaka	Prabhava	Karma
Tikta (~Bitter), Kashaya (~Astringent)	Laghu (~Light), Snigdha (~Untuous)	Ushna (~Hot)	Madhura (~Sweet)	Vishaghna (~Anti-Toxic)	Tridosha Shamaka (~pacifies the three regulatory functional factors of the body)

Therapeutic Properties referred in Nighantus

Karmas (Action)	D.N.	S.N.	M.N.	R.N.	K.N.	B.N.	AN	MaN	RVN	LN
Rasayana (~rejuventor)	-	-	+	-	+	+	-	+	+	+
Jwarahara (~anti-pyretic)	+	+	+	+	+	+	+	+	+	+
Sangrahi (~absorbent)	+	-	+	-	+	+	-	+	+	+
Dipana (~digestive)	-	+	+	-	+	+	+	+	+	+
Amahara (~treats indigestion)	-	-	-	-	+	+	-	-	-	-
Vayasthapana (~prolonging younger age)	-	-	-	-	+	-	-	-	-	-
Pramehaghna (~anti-diabetic)	+	-	-	+	+	+	-	-	-	-
Kushtaghna (~anti-dermatosis)	+	-	+	-	+	+	-	-	-	-
Balya (~strength promoting)	+	-	+	-	+	+	-	-	+	-
Medhya (~intellect enhancer)	+	-	-	-	+	-	-	-	-	-
Kasahara (~anti-tussive)	-	-	-	-	+	+	-	-	-	-
Hridya (~beneficial for heart)	-	-	-	-	+	-	-	-	-	-
Krimighna (~anti-helminthic)	+	-	+	-	+	+	-	-	-	-
Chakshushya (~beneficial for eye)	-	-	-	-	-	-	-	-	-	-
Arshoghna (~anti-haemorrhoidal)	+	-	-	-	-	+	-	-	-	-

Karmas (Action)	D.N.	S.N.	M.N.	R.N.	K.N.	B.N.	AN	MaN	RVN	LN
Vata raktahara (~beneficial in gout)	+	-	+	+	+	+	-	+	-	+
Kamala (~jaundice)	-	-	+	-	+	+	-	+	+	+
Pandu (~anemia)	+	-	-	+	+	+	-	-	-	-
Trishnahara	-	-	-	-	-	-	+	-	-	-
Chardighna	+	-	-	-	-	+	+	-	+	-
Shwasahara	-	-	-	-	-	+	-	-	-	-
Hridroga	-	-	-	-	-	+	-	-	-	-

DN: Dhanvantari Nighantu
MN: Madanapala Nighantu
AN: Ashtanga Nighantu
SN: Saushruta Nighantu
KN: Kaiyyadeva Nigantu
MaN: Madanadi Nighantu
RN: Raja Nighantu
BN: Bhava Prakasha Nighantu
RVN: Raja Vallabha Nighantu
LN: Laghu Nighantu

A few therapeutic applications as mentioned in classical literature:

1. Jvara (~Fever):

1. Decoction of the cold infusion of *Guduchi* should be taken[14].
2. Juice of *Guduchi* and *Shatavari* in equal quantity mixed with jaggery alleviates fever caused by *Vata*.[14]
3. *Guduchi* juice alone checks fever caused by *vata* (~one of the three bodily humors).[15]
4. The juice of *Guduchi* mixed with *Pippali* checks fever.[16]
5. Cold infusion of *Guduchi* mixed with sugar alleviates fever caused by *pitta* (~one of the three bodily humors).[17]
6. Decoction of *Guduchi, Parpata* and *Amalaki* overcomes fever caused by pitta.[18]
7. Oil prepared with powder of *Katuki* (*Picrorhiza kurroa* Royle ex Benth) or leaves of *Guduchi* or *Sahadevi* (*Sida rhombifolia* L.) juice alleviates fever.[19]

2. Vishama Jvara (~Fever of irregular pattern)

1. Decoction of *Triphala* (Combination of three fruits viz. ***Terminalia chebula, Terminalia bellerica*** and ***Emblica officinalis)*** or juice of *Guduchi* is useful.[20]
2. One should take the decoction of *Guduchi, Nimba* (*Azadirachta indica* A. Juss) and *Amalaki* (*Emblica officinalis* Gaertn) mixed with honey.[21]
3. *Guduchi modaka*.[22]

3. Jirna Jwara (~Chronic fever):

1. *Ghrita* (Medicated ghee) and oil (Medicinal oil) prepared with juice and paste of *Guduchi, Triphala, Vasa* (***Justicia adhatoda*** L), *Draksha* (*Vitis vinifera* L.) and *Bala* (*Sida cordifolia* L.) alleviate fever.[23]
2. Decoction of *Guduchi* added with *Pippali* (*Piper longum* L.) powder destroys chronic fever and *Kapha* (~one of the three bodily humors).[24]
3. Cold infusion of *Guduchi* alleviates chronic fever.[25]
4. One should use *Guduchi* juice mixed with *Pippali* powder and honey to treat chronic fever, spleen enlargement, cough and anorexia. [26]
5. In case of vomiting in fever, cold decoction of *Guduchi* mixed with honey should be taken.[26]
6. The leaves of *Guduchi* should be used as vegetables in fever.[27]

4. Kamala (~Jaundice) and Halimaka (~Hepatitis)

1. One suffering from jaundice should take buffalo's ghee processed with *Guduchi* juice and milk.[28]
2. The patient of jaundice should take decoction of *Triphala* or *Guduchi* or *Daruharidra* (*Berberis aristata*) or *Nimba* mixed with honey in the morning.[29]

5. Chardi (~Vomiting)

1. In case of vomiting, a decoction of *Guduchi* should be taken.[30]
2. Decoction of *Guduchi, Triphala, Nimba* and *Patola* (*Tricosanthes dioicia* Roxb.) mixed with honey and sugar alleviates vomiting and *Amplapitta* (Hyperacidity).[31]
3. Cold infusion of *Guduchi* mixed with honey checks severe vomiting caused by three *doshas*.[32]

6. Amlapitta (~Hyperacidity)

- Decoction of *Guduchi, Nimba* and *Patola* leaves mixed with honey alleviates *Amlapitta*.[33]

7. Vatarakta (~Gout)

1. *Guduchi* is useful in the management of *Vatarakta*, *Halimaka*, *Pandu, Kamala*, and *Sthaulya*.[34]
2. *Guduchi* is said to be the best remedy in the management of *Vatarakta*.[35] It has been advised to take *Guduchi* decoction processed in *Ghrita* or Milk.[36] *Guggulu* along with *Guduchi* decoction is said to be beneficial.[37] Formulations with the name of *Amritadya taila*,[38] *Madhuparnyadi taila*,[39] *Guduchi ghrita*,[40] *Amrtaghrita*,[41] and a decoction of *Guduchi*[42] are referred in the management of the disease.
3. Oil prepared with a decoction of *Guduchi* and milk or *Draksha* decoction, or decoction of *Madhuka* and *Kashmarya* alleviates *Vatarakta*.[38]
4. Decoction prepared with 30 g of *Guduchi, Shunthi,* and *Dhanyaka* alleviates *Vatarakta, Amavata* and all types of *Kushtha*.[43]

8. Amavata (~Rheumatism)

Guduchi taken along with the *Shunthi* alleviates *Amavata.*[44]

9. Kushtha (~Various Skin Diseases)

Juice or decoction or ghee processed with *Guduchi* alleviates all types of skin diseases.[45]

10. Kasa (~Cough)

Guduchyadi ghrita alleviates cough.[46]

THERAPEUTIC USES DESCRIBED IN OTHER SYSTEMS OF MEDICINE

Siddha:

Coṟi (~Pruritus), Curam (~Fever), Kaya noy (~Tuberculosis), Kuruti alal (~Bleeding disorders), Kuttam (~Hansen's/skin diseases), Mekam (~Genital diseases), Pinicam (~Sinusitis).[47]

Unani:

Humma (~Fever), Ishal (~Diarrhoea), Zaheer (~Dysentery), Deedan-e-Ama (~Worm infestation).[48]

Part Used:

Stem

Dose:

3 - 6 g of Giloy in powdered form along with specified adjuvants

20 - 30 g of Coarse powder for preparing decoction

125 mg - 1000 mg of Guduchi satva along with specified adjuvants

IMPORTANT FORMULATIONS

Ayurveda

Amritarishta (AFI, Part I, 1:2)

Amritottara Kvatha Churna (AFI, Part I, 4:1)

Guduchi sattva (AFI, Part I, 14:1)

Chinnodbhavadi Kvatha Churna (AFI, Part I, 4:7)

Kaishora Guggulu (AFI, Part I, 5:2);

Guduchyadi Taila (AFI, Part II, 8:5).

Brihat Guduchi Taila (AFI, Part I, 8:38).

Samshamani Vati/Guduchi Ghana Vati (AFI, Part II, 10:13)

Guduchi Lauha (AFI, Part II, 17:1).

Unani:

Sufoof-e-Satt-e-Gilo, Sufoof-e-Satt-e-Gilo-Sartani (UPI, Part I, Vol I 2007)

Siddha:

Cintil Curanam, Cintil Ney, Kapa Curak Kutinir (SPI, Part I, Vol I 2008)

IMPORTANCE OF BOTANICAL IDENTITY

The genus *Tinospora* includes 34 species,[9] however, phytochemical investigations, pharmacological experiments, and clinical applications have mainly focused on four species of *Tinospora,* viz. *T. cordifolia, T. sagittata, T. capillipes,* and *T. crispa*.

Tinospora cordifolia (TC) has been reported to effectively prevent hepatotoxicity,[49] whereas certain other species like *Tinospora crispa* may be associated with hepatotoxicity. [50] Thus, consumption without correctly identifying the plant might land in hepatic injury. Thus, proper identification becomes a mandate. Considering this, the Ministry of Ayush has released an advisory, and urged ASU manufacturers and ASU drug associations to comply with the Pharmacopoeial Standards of *Guduchi* before its use in various formulations. [51]

The characteristic features of *T. cordifolia* and *T. crispa* are:

Plant part	Tinospora cordifolia	Tinospora crispa
Leaf shape	Broadly ovate	Broadly ovate to suborbicular
Epicuticular wax	Present on both surfaces of the leaf	Absent
Tyloses in the vessels of the stem	Observed	Not observed
Stem	Green in colour Not having small rounded projections No milky secretion	Greenish grey in colour Having small rounded projections Milky secretion
Leaves	Heart-shaped with a groovy notch at the base	Heart-shaped with no groovy notch at the base
Petals	Six in number	Three in number
Drupes	Spherical or ball-shaped Red in colour	Ellipsoid or rugby ball-shaped Orange in colour
Photograph of the plant		

IDENTIFICATION:

Parts used:

Stem

A) **Macroscopy:**

Drug occurs in pieces of varying thickness ranging from 0.6-5 cm in diameter. Young stems are green in color with smooth surfaces and swelling at nodes, and older ones show a light brown surface marked with warty protuberances due to circular lenticels; transversely smoothened surface shows a radial structure with conspicuous medullary rays traversing porous tissues. It tastes bitter.

B) **Microscopy:**

Transverse section of stem shows outer-most layer of cork, differentiating into outer zone of thick-walled brownish and compressed cells, and inner zone of thin walled colourless, tangentially arranged 3-4 rows of cells. Cork is broken at some places due to opening of lenticels, followed by 5 or more rows of secondary cortex of which the cells of outer rows are smaller than the inner one. Just within the opening of lenticels, groups of sclereids consisting of 2-10 cells are found in the secondary cortex region. Outer zone of the cortex consists of 3-5 rows of irregularly arranged, tangentially elongated chlorenchymatous cells. Cortical cells are situated towards the inner side, which are polygonal in shape and filled with plenty of starch grains. They are simple, ovoid, or irregularly ovoid-elliptical, occasionally composed of 2-4 components. Several secretory cells are found scattered in the cortex with pericyclic fibres lignified with wide lumen and pointed ends, associated with a large number of crystal fibres containing a single prism in each chamber. Vascular zone is composed of 10-12 or more wedge-shaped strips of xylem, externally surrounded by semi-circular strips of phloem, alternating, with wide medullary rays. Phloem consists of sieve tube, companion cells and phloem parenchyma of polygonal or tangentially elongated cells. Some of them contain crystals of calcium oxalate, and cambium is composed of one to two layers of tangentially elongated cells in each vascular bundle. Xylem consists of vessels, tracheids, parenchyma and fibres. In primary xylem, vessels are comparatively narrow devoid of tyloses. Secondary xylem elements are thick-walled, lignified, and vessels are cylindrical in shape and bearing bordered pits on their walls. Some large vessels possess several tyloses and often contain transverse septa, and meduallry rays which are 15-20 or more cells wide containing rounded, hemispherical, oblong, ovoid, with faintly marked concentric striations and central hilum appearing like a point. Starch grains of 5.5-11.20 µ in diameter and 6-11.28 µ in length are present in the pith composed of large, thin-walled cells mostly containing starch grains.

Physico-chemical profile: [52]

- Foreign matter:
  Not more than 2 per cent
- Loss on drying:
  Not more than 10 per cent
- Total ash:
  Not more than 16 per cent
- Acid-insoluble ash:
  Not more than 3 per cent
- Alcohol-soluble extractive:
  Not less than 3 per cent
- Water-soluble extractive:
  Not less than 11 per cent

Assay of Major Chemical Constituents: *Guduchi* contains not less than 0.02% w/w of cordifolioside A and the percentage of tinosporaside ranges from 0.03 to 0.04. [53-54]

Other Chemical Constituents: The other components are Tinosporin, Tinosporon, Tinosporic Acid, Tinosporol, Tinosporide, Tinosporidine, Columbin, Chasmanthin, Palmarin, Berberine, Giloin, Giloinisin, 1-2, Substituted Pyrrolidine, a Diterpenoid Furanolactone, 18- Norcleropdanedditerpine-O- Glucoside, Aryltetrahydrofuranolignan, Octacosanaol, Nonacosan-15-one and β - Sitosterol, Cordifolide, Unosporin, Heptacosanol, Cordifolon, Cardifolon, Magnoflorine, Tembetarine, Cardiofolisides A & B, Phenolic Lignan-3 - (α, 4- Dihydroxy-3-methoxybenzyl) - 4- (4-hydroxy -3- methoxybenzyl) - tetrahydrofuran, Arabinoglactan (various parts).[11]

TLC fingerprint of *Tinospora cordifolia:*[55]

Stationary phase : TLC precoated plate with Silica gel 60 F_{254} of 0.2 mm thickness.

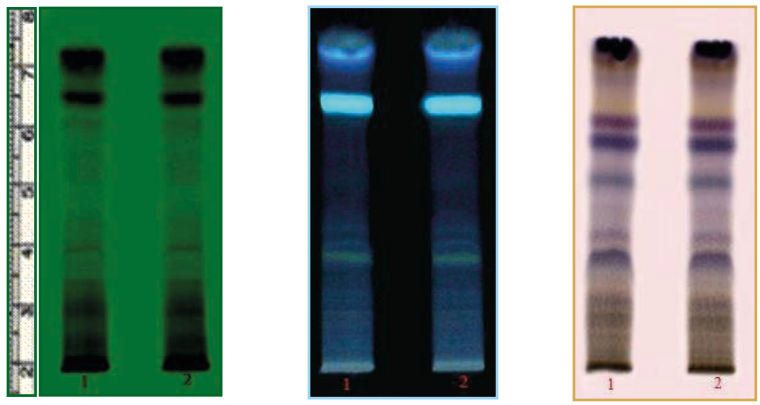
Solvent system : *Chloroform: Methanol (9:1)*

Volume of test solution applied : 7 µl

Distance travelled by solvent system : 8 cm

Development chamber : Twin trough chamber (10 x 10 cm) with SS lid.

Visualization : under 254 nm; under 366 nm; after derivatization with Anisaldehyde - Sulphuric acid [254 nm - major spots at Rf 0.79 and 0.93 (both dark grey); 366 nm - major spots at Rf 0.30 (yellow), 0.75 (bright sky blue) and 0.88 (blue); After derivatization - major spots at Rf 0.35, 0.57, 0.67 and 0.73 (all violet).



TLC fingerprint of test solution of Tinospora cordifolia

1 : Test solution of T1,	I :	254 nm,
2 : Test solution of T2	II :	366 nm,
	III :	After derivatization

SUMMARY AND EXCERPTS OF RESEARCH STUDIES

Tinospora cordifolia (TC) is a widely used plant in the Ayurvedic system of medicine. There are several research studies conducted on this plant both clinical as well as preclinical and analytical. It has shown potential as an immunomodulatory, anti-inflammatory, anti-diabetic, anti-oxidant, and various other pharmacological properties useful to mankind.

During the COVID-19 pandemic, TC has been widely used as a medicine for prevention as well as therapeutic management. Despite its pharmacological importance, many recent clinical studies have highlighted the potential hepatotoxic behavior of TC. It was first reported by *Nagral et al.* (2021) that on consuming TC for an average of 90 days, six patients presented with symptoms of acute hepatitis during the study period of four months during the COVID-19 pandemic. The patients during the study period exhibited signs of critical liver injury, but also recovered after the withdrawal of TC consumption. Due to these observations, they reached the conclusion that TC consumption may have induced an autoimmune-like hepatitis condition or unmasked an underlying autoimmune chronic liver disease, due to the immune stimulant mechanism of the herb. They also recommended that caution should be exercised during the use of this herb, especially in those predisposed to autoimmune disorders. [56]Similarly, three cases of suspected Ayurvedic medication-associated liver injury were observed at a Southern California community hospital. These patients presented with acute hepatocellular injury and jaundice after taking Ayurvedic supplements i.e. *Giloy Kwatham, Manjishthadi Kwatham*, *Aragwadhadi Kwatham,* and *Kanchnara Guggulu* respectively for 90-120 days. They observed that the aminotransferase activities decreased to 50% in < 30 days and hence highlighted the risk of drug-induced liver injury from Ayurvedic medications. [57]

Subsequently, few other reports were published, explaining the similar behavior in patients on TC consumption. A large retrospective Indian multicenter study spanning 13 centers at nine locations was designed to identify features and outcomes of herb-induced liver injury (HILI), temporally associated with *Giloy* use. They evaluated the chemical and toxicological properties and reported that 43 patients presented with acute hepatitis, acute worsening of chronic liver disease (CLD, the most common clinical presentation), or acute liver failure after a median consumption of 46 days. Hence, they concluded that *Giloy* consumption is associated with acute hepatitis with autoimmune features and can unmask autoimmune hepatitis (AIH) in people with silent AIH-related CLD. [58]

In its support, a different study discussed three cases where the liver injury was severe, requiring transjugular liver biopsy to aid the diagnosis. They concluded that two of their patients had associated autoimmune diseases - hypothyroidism in patient 1 and SLE & hypothyroidism in patient 3. They suspected possibility that the immune-stimulant effects of *T. cordifolia* would have led to autoimmune-like hepatitis in patient 1, and the unmasking of latent chronic auto-immune liver disease in patient 3. Hence, they concluded the need to urge caution and a warning about *T. cordifolia*-

related liver toxicity, especially in high-risk subjects with associated autoimmune disorders.[59-60] Another study also stated that if there are continued reports of liver injury associated with TC consumption, the hepatology community should consider a systematic approach to investigate the risk factors and optimal ways to mitigate the risk.[61]

Despite these reports, *Balkrishna et al*. debated the work of *Nagral et al*. in a letter-to-editor, by stating that the study showed several knowledge gaps. They highlighted the importance of proper recording of the medical history in patient-related case reports, as they elucidate the past disease modalities and the baseline level for the measured biomedical parameters. They stated that any additional medication taken by the patients or their liver function status before the patients started taking *T. cordifolia* is important and these were not reported.[62]

In the Ayurvedic as well as other Indian medical systems literature, however, there are several uses of *Guduchi* or Giloy described and it has been successfully used in clinical practice. Also, research publications provide evidence for its safety and efficacy. Many studies have reported the anti-toxic nature of *Tinospora cordifolia* (TC) and it has been well demonstrated that TC does not exert any remarkable adverse effects on the cardiovascular system, renal system,[63-65] central nervous system,[63, 66-69] and gastrointestinal system.[70-72]

To understand and explain the therapeutic benefits and safety of TC; a systematic literature search has been carried out on *Guduchi* or Giloy from Ayurveda and research publications available on PubMed on *Tinospora cordifolia* (TC) as of March 2022. It was found that a large spectrum of research publications such as on safety, toxicity, and efficacy evaluation in diverse disease or health conditions (Figure 1) as well as type of studies such as analytical to preclinical and clinical can be found (Figure 2). TC has been tested either as a single herb or as a component of the multiherbal formulations. Also, TC extracts in different solvents are also analyzed for their effect in different models (Figure 3)

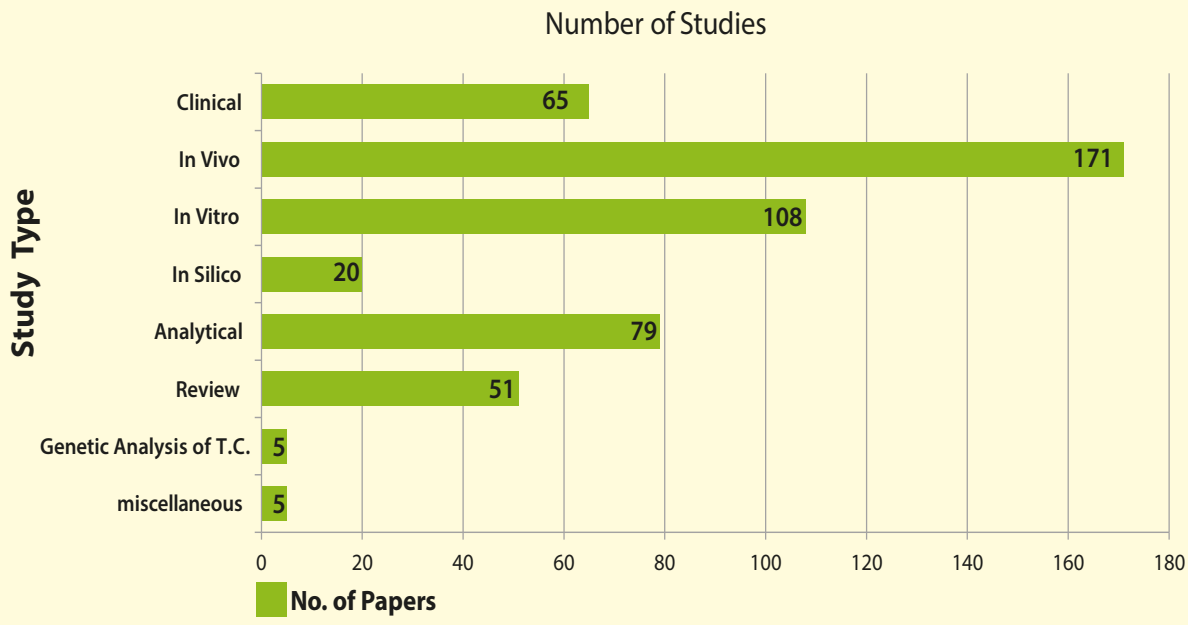


Figure.1. Categorization of articles on the basis of study type

A total of 499 studies were categorized into 7 study types. Articles demonstrating pre-clinical and clinical trials in the same study were accounted in both the study types. The clinical studies included human clinical trials and case studies. The In-Vivo studies included studies conducted on rats (52), mice (28), Drosophila (3), Cows (2), and Shrimp (1). A total of nine studies were not included in the categorization as the full papers were not available or the articles were retracted. The miscellaneous category comprising five articles related to environmental and bio-fabrication methods were also not included in the representation as they were not relevant to the present context.

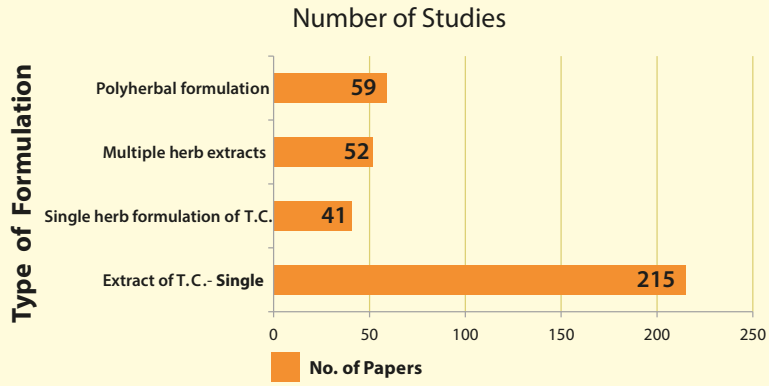


Figure.2. Categorization of articles based on the type of formulation/intervention used

Based on the type of formulation used in studies, a total of 367 studies were identified and were classified into four categories. Articles in which *T. cordifolia* was not studied or review articles describing the morphology, chemistry, or pharmacology of the plant were also not included for representation.

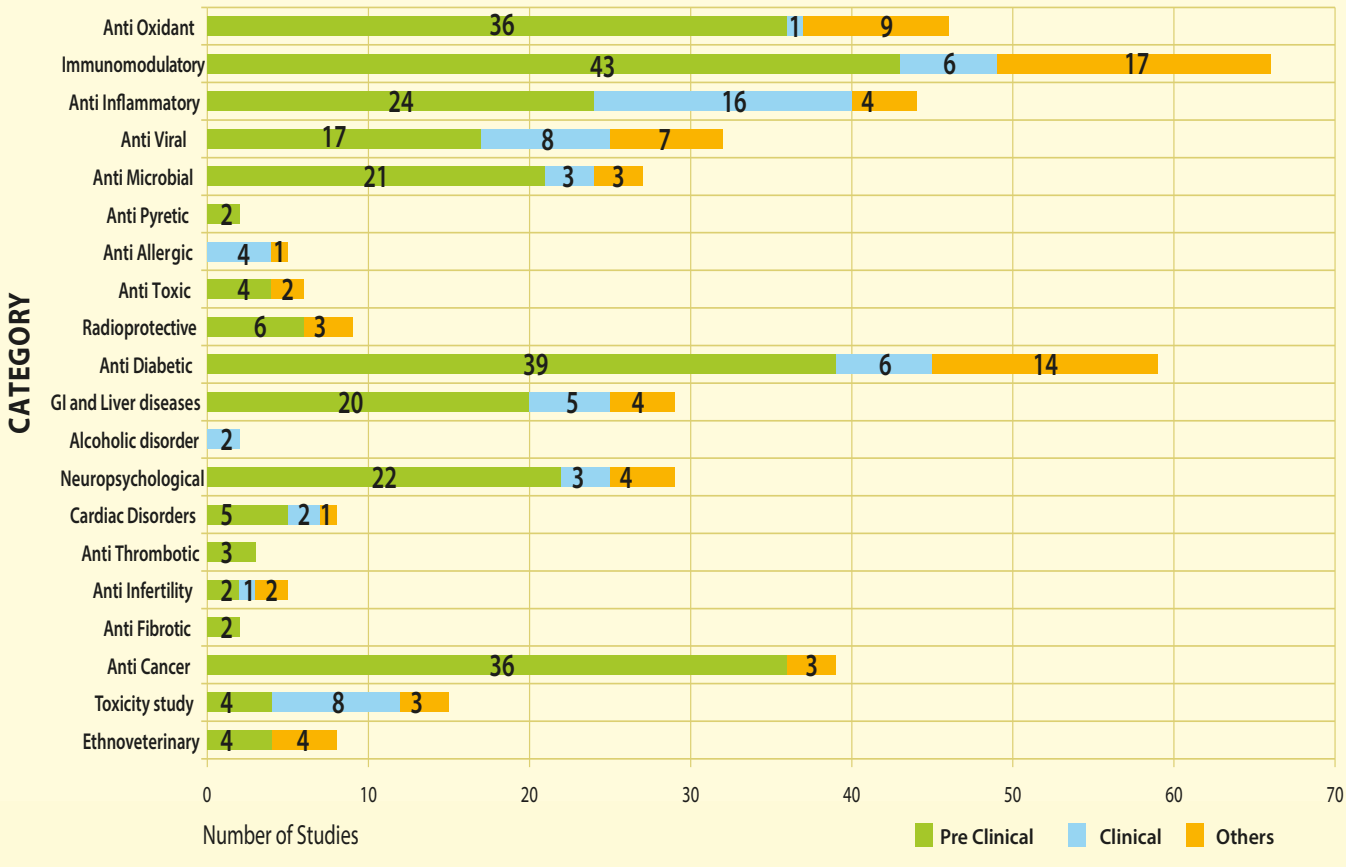


Figure.3. Categorization of articles based on the condition/effect studied

The studies were grouped into 23 categories based on the condition/effect studied. Articles reporting pre-clinical trials (In-Silico, In-Vivo, and In-Vitro studies) and Clinical trials are represented in the chart. Of these 23 categories, the categories namely, Medicinal, Chemical Analysis, and Genomic studies were not represented in the chart as no pre-clinical studies or clinical studies were conducted in the specified categories. A total of 12 articles in the Medicinal category, one study in the Genomic analysis, and 51 studies in the Chemical Analysis category were identified. Studies represented with the heading "Others" comprise of either a review article, letter to the editor, or analytical studies describing the pharmacology of the herb *T. cordifolia.*

Amongst the Vivo studies, TC has been tested in different animal species-related disease models such as mice, rats, drosophila, zebrafish, and monkeys. Some of the veterinary applications are also found.

As regards toxicity evaluation there are studies done on pre-clinical models as well as clinical phase I and II. Additionally, the safety of TC can be inferred also from efficacy-related clinical studies where no adverse effects are reported.

These include a comparative evaluation of TC with conventional treatment (e.g. in osteoarthritis) OR as adjuvant with conventional treatment. (e.g. with Anti Koch's treatment as hepatoprotective agent). In either of them, no remarkable adverse effects are reported. In addition to this, data on its widespread use globally as well as in folklore medicine with other medications or stand-alone also could throw light on its safety in diverse clinical contexts.

Although there is a higher number of preclinical reports than clinical, and clinical studies are also carried out on diverse conditions and in diverse protocols, more multicentric, targeted safety and toxicity studies, both short term and long term as well as herb-drug interaction studies may be undertaken. Although there are reports suggesting the beneficial role of TC in Auto-immune disease models such as EAE (Experimental Autoimmune Encephalo-myelitis) and RA (Rheumatoid Arthritis) related models, studies to evaluate the role of TC in pre-existing auto-immune disease models or other co-morbidity conditions with and without concurrent drug use; may provide definite answers as regards speculated toxicity in patients with clinical AIH and HILI.

Some of the salient findings reported in these studies are described below, highlighting the clinical spectrum of this herb and its formulations.

PRECLINICAL SAFETY & EFFICACY STUDIES

To explore the possible genotoxic risk of *Tinospora cordifolia* (TC), study was performed through Ames test, in-vitro chromosome aberration assay, in-vivo rodent bone marrow micronucleus (MN) assay, and Comet assay. Experimental results confirmed that in the Ames test, upto 5000 lg/plate of TC did not exhibit any mutagenic effect in *Salmonella typhimurium* mutant strains (TA97a, TA98, TA100, TA102, and TA1535). In chromosome aberration assay, TC was not clastogenic to human peripheral blood lymphocytes up to a concentration of 3000 lg/ml. In MN and Comet assays, TC was pre-treated for seven 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. In conclusion, the results of four genotoxicity models clearly confirmed that aqueous extract of *T. cordifolia* was devoid of genotoxic effect under the said experimental conditions.[73]

Acute toxicity study with the dose of 3 g/kg demonstrated that *T. cordifolia* does not have any side effects and reported no death of the experimental rats.[67] When administered in doses of 0.1 g/kg for 12 weeks, *T. cordifolia* does not trigger any unfavorable factors 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.[74] The LD_{50} value for *T. cordifolia* is higher than 1 g/kg for oral administration.[71]

The non-clinical safety of Coronil (a formulation containing TC)was demonstrated in a 28-day repeated dose toxicity study along with a 14-day recovery period in Sprague Dawley rats. The tested Coronil dose levels were 0, 100, 300, and 1000 mg/kg/day, orally administered to 5 males and 5 female rats per test group. No mortality was observed in any group, and in addition, Coronil did not elicit any finding of toxicological relevance with respect to the studied clinical chemistry parameters, as well as macro- or microscopical changes in any organs, when compared to the control group. The acceptable safety profile of Coronil paves way for further toxicity assessments in rodents for a longer duration as well as in higher animals, and towards its clinical investigation.[75]

TC is reported to boost the phagocytic activity of macrophages, production of reactive oxygen species (ROS) in human neutrophil cells, enhances nitric oxide (NO) production by stimulating splenocytes and macrophages suggesting its anti-tumor effects. TC aqueous extracts has been reported to influence the cytokine production, mutagenicity, **stimulation and activation of immune** effector cells. In-vitro evidences have shown that it up-

regulates the IL-6 cytokines facilitating the acute response to injuries, inflammation, activation of cytotoxic T cells and also B cell differentiation. [76-78] Reports on *Tinospora cordifolia* in prevention of oxidative damage also exist. Synergistic effects of compounds in the immunomodulatory activity of *Tinospora cordifolia* are reported. [79] TC exhibit **anti-toxin** effect due to its antioxidant property. It has been reported to scavenge free radicals generated during aflatoxicosis. [80] The **anti-oxidant capacity** of *Tinospora cordifolia* stem methanol extracts administered orally increased the erythrocytes membrane lipid peroxide and catalase activity. It also decreased the activities of SOD, GPx in alloxan-induced diabetic rats. [81]

TC has HIV protease inhibitor activity, and it is reported to interfere with the gp120 / CD4 interaction and inhibit HIV-reverse transcriptase showing its **anti-viral efficacy** for HIV. [82,83] TC aqueous extract was evaluated for Infectious bursal disease (IBD) of young chicks caused by infectious bursal disease virus (IBDV) and found to significantly reduce the mortality rate and **enhancing the immunity**. [84] Based on virtual screening and molecular docking analysis, the phytochemical compounds, namely tinosponone, xanosporic acid, cardiofolioside B, tembetarine and berberine of *T. cordifolia* were identified as possible lead molecules to fight against **SARS-CoV-2.** The in-silico study proved that tinosponone as potent, selective and nontoxic inhibitor of 3CL protease of SARS-CoV-2. [85]

Pre-clinical hepato-protective activity

Nipanikar et al. conducted an animal study by inducing liver toxicity through carbon tetrachloride, ethanol, and paracetamol. Seven groups of albino-Wistar rats were studied for low, medium, and high dosages of a polyherbal formulation AHPL/AYTAB/0613 tablet [containing extracts of *Bhringaraja* (*Eclipta alba*), *Guduchi* (*Tinospora cordifolia*), *Daruharidra* (*Berberis aristate*), *Kakamachi* (*Solanum nigrum*), *Punarnava* (*Boerhaavia diffusa*), *Bhumyamalaki* (*Phyllanthus niruri*), *Kutaki* (*Picrorhiza kurroa*), and *Kalamegha* (*Andrographis paniculata*)] in comparison with silymarin and a marketed polyherbal drug. The authors found out that the tablet has significant hepatoprotective activity. [86]

Studies have also been performed to elucidate the pharmacological role of TC in chronic liver damage in rats and goats. The study shows that the anti-fibrotic property of the herb was mediated through the activity of Kupffer cells, as depicted by the carbon clearance test parameter. The anti-hepatotoxic activity of TC has been demonstrated in CCl_4 induced liver damage, normalizing liver function as assessed by morphological, biochemical (SGPT, SGOT, serum alkaline phosphatase, serum bilirubin) and functional (pentobarbitone sleep time) tests. [87-88]

Singh et al. reported the hepatoprotective effect of a polyherbal formulation on paracetamol-induced hepatotoxicity in albino rats in their in-vivo study. The polyherbal formulation contained *Andrographis paniculata*, *Tinospora cordifolia,* and *Solanum nigrum* in the ratio of 2:1:1. The authors concluded that the formulation was not only effective for the management of liver ailments but also for the lipid profile. [89]

Another study was conducted by *Panchabhai et al*. to evaluate the hepatoprotective effect of *Tinospora cordifolia* and *Phyllanthus emblica* in combination against hepatic damage induced by anti-tubercular drugs in rat models. The authors concluded that the herbs exerted a synergistic protective effect when co-administered with anti-tubercular drugs. [90] The extracts have further been shown to be useful in reversing metabolic derangements in chronic alcoholism without any major adverse effect. [91]

Pre-clinical nephro protective activity

Similarly, a study to indicate the cellular lipid peroxidation by free radical responsible for acute renal failure induced by gentamicin (GM) was also carried out. Here, sixty rats were divided into six equal groups to evaluate the role of TC. Gentamicin (80mg/kg/day for 7 days) was administered to produce nephrotoxicity and structural alterations were evidenced from histopathology of renal tissues which indicated the renal injury and dysfunction in rats. The ethanol extract of TC (200mg/kg/day) was administered with gentamicin simultaneously and also sequentially to observe preventive and curative effects respectively. Both the groups recovered from the gentamicin-induced nephrotoxicity, evidenced by improvement of histopathological features, though accurate mechanism and safety profile are not confirmed by this study. [92] It is shown to have nephro protective properties against the aflatoxins induced toxicity. [93] It is also found to be beneficial in overcoming the Cyclophosphamide induced toxicities during cancer treatment. [94]

In an interesting study by *Bahadur, S. et al*., the inhibition potential of *T. cordifolia* extracts and its constituent Tinosporaside to cause herb-drug interactions through rat and human liver cytochrome enzymes were evaluated. It was observed that the content of Tinosporaside was found to be 1.64% (w/w) in TC extract. Concentration-dependent inhibition was observed through TC extract. Observed IC_{50} (µg/ml) value was 136.45 (CYP3A4), 144.37 (CYP2D6), 127.55 (CYP2C9), and 141.82 (CYP1A2). Tinosporaside and extract showed a higher IC_{50} (µg/ml) value than the known inhibitors. *T. cordifolia* extract showed significantly less interaction potential indicating that the selected plant has no significant herb-drug interactions relating to the inhibition of major CYP450 isozymes. As a conclusion to this study, it was stated that the plant extract showed a significantly higher IC_{50} value than respective positive inhibitors against CYP3A4, 2D6, 2C9, and 1A2 isozymes and that the consumption of *T. cordifolia* may not cause any adverse effects when consumed along with other xenobiotics. [95]

As toxicity analysis is an important aspect of pharmacology, an acute oral toxicity in-vitro assessment was conducted in RAW 264.7 macrophages, which were pre-incubated with chloroform extract of TC (CETC) and subsequently stimulated with bacterial lipo-polysaccharide (LPS). The LPS-induced upregulation of proinflammatory biomarkers was significantly prevented by CETC, without inhibiting COX-1. The anti-inflammatory potential of CETC was validated further in a rat model of carrageenan-induced hind paw edema. It was observed that even with a high dose there were no obvious toxic or deleterious symptoms. The LD_{50} of CETC was reported to be above 2000 mg/Kg body weight. [96]

Sharma et al. in their in vivo study on Swiss albino mice demonstrated hepato-protective effect of *T. cordifolia* against lead nitrate induced toxicity. The aqueous stem and leaf extract were used and the authors concluded that the herb is capable of scavenging the free radicals generated due to lead induced toxicity. [97]

In a study by *Bishayi et al,* the hepatoprotective and immunomodulatory property of *T. cordifolia* was studied in CCl_4 intoxicated albino rats. The herb in the form of *Satwa* was administered for a period of 15 days in the dose 100mg/Kg/BW. At the end of the study, the liver enzymes were studied and it was observed that levels of Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Alkaline Phosphatase (ALP) and bilirubin were significantly reduced. [98]

Chavan et al. studied the hepatoprotective activity of *satwa* of *Tinospora cordifolia*, *Tinospora sinensis* and *Neem-guduchi* against alcohol-induced liver injury in albino Wistar rats. The authors observed in their study that the combination of *Satwa* of three herbs acts as a liver tonic and helps to restore and strengthen liver functions. [99]

Adhvaryu et al. evaluated the hepatoprotective and immunomodulatory activity of four Indian medicinal herbs namely *Curcuma longa* (CL), *Oscimum sanctum* (OS), *Tinospora cordifolia* (TC) and *Zizyphus mauritiana* (ZM) on induced liver injury and immunosuppression caused by anti-tubercular drugs namely Isoniazid (INH), Rifampicin (RIF) and Pyrazinamide (PZA). The study was conducted on guinea pigs showed a hepatoprotective effect and prevented immunosuppression. The highest hepatoprotection observed was that of *Curcuma longa* and *Tinospora cordifolia* and the strong immunomodulatory activity was that of *Tinospora cordifolia* and *Zizyphus mauritiana*. [100]

Additionally, other *Tinospora* species known as *crispa* has shown toxic effects on liver which is frequently intermixed with *cordifolia* species due to their similar resemblance. [50, 101] People might suffer from hepatic injury or even death if they consume the herb without correctly identifying these two species.

Pre-clinical radio-protective activity

There are reported studies that have assessed the radioprotective effect of TC. Study of *Goel et al.* assessed the radioprotective potential of *T. cordifolia* against gamma radiation exposure to mice. The radioprotective efficacy of the herb in terms of spleen colony-forming units (CFU), cell cycle progression, hematological parameters, micronuclei induction, and whole-body survival were assessed. [102] The results of the study were in concordance with a similar study, conducted by *Pahadiya et al*, wherein, a sub lethal dose of gamma radiation on Swiss albino mice was used to study the effect of aqueous extract of *T. cordifolia*. The authors concluded that the herb has a radioprotective effect against gamma radiation exposure. [103] A similar study conducted on Swiss albino mice by *Sharma et al*, demonstrated the protective effect of *T. cordifolia* administration on radiation-induced dystrophies. The authors concluded from their study that a dose of 75mg/Kg/BW/day was found to be the optimum dose for radioprotective effect. [104]

Neuro-Protective activity

Neuro-protective effect of *T. cordifolia* was assessed in a study by *Birla et al* in a Parkinsonian mouse model with intoxication by Rotenone (ROT). The study also explored the mechanism of action responsible for the restoration of levels of various protein molecules through the proteomics and qRT-PCR approach. The therapeutic effect of the herb is observed due to the regulation of various signaling pathways which protect the dopaminergic neurons and restores the mitochondrial function. [105]

To study the anti-depressant activity of *T. cordifolia*, *Dhingra et al* conducted a study in Swiss albino mice by administering petroleum ether extract of *T. cordifolia* in 3 doses (50, 100 and 200 mg/kg, P.O.)

administered for 14 successive days. The parameters used were Tail suspension test (TST) as well as in Forced swimming test (FST). The study concluded that there was the involvement of Monoaminergic and GABAergic Systems in the Antidepressant-like activity of *Tinospora cordifolia*. [106]

The anti-diarrheal and anti-ulcer properties of the extracts of *T. cordifolia* were explored by *Kaur et al* in rat models. The aqueous and ethanolic stem bark extracts administered in doses of 250 and 500 mg/kg doses were found to reduce the frequency of loose stools and showed a dose-dependent anti-diarrheal effect. With the reduction in ulcer index, total acidity and decreased gastric volume, and an increase in gastric pH, the antiulcer activity of the herb was established. [107]

The intestinal motility enhancing property of *T. cordifolia* in combination with *Zingiber officinale* and *Terminalia chebula* has been explored by *Patel et al* in Swiss albino mice. The formulation was found to be useful in gastric problems without affecting general physiology. [108]

CLINICAL REPORTS ON TINOSPORA CORDIFOLIA

Safety Profile-related studies

In a clinical study, the safety profile of TC was evaluated in healthy volunteers using a battery of hematological and biochemical tests and by an open questionnaire method. This was performed on thirty healthy volunteers who participated in a randomized, double-blinded, placebo-controlled design study for 21 days. The safety assessment was done with the help of hematological and biochemical investigations, which were assessed before and after the medication by unpaired t-test. It was concluded that TC is safe at a dose of 500mg per day for a period of 21 days in healthy volunteers. [109]

Kuchewar et al. conducted a randomized double-blind study to assess the effects of *Ashwagandha* and *Guduchi* on 30 healthy individuals to understand the antioxidant potential of the herbs. The subjects consumed 500mg of the drug in capsule form two times a day orally with water for a period of 6 months. Before and after the treatment, the parameters such as hemoglobin%, Erythrocyte Sedimentation Rate (ESR), Super-Oxide Dismutase (SOD) level, Malondialdehyde (MDA), etc., were assessed. The authors concluded that the herbs possess antioxidant potential. Also, the authors stated that both the drugs were safe for young adults when administered at given doses and for the specified duration. [110]

Sarokte et al. conducted an open, prospective, randomized clinical trial on 90 school going children to assess the effect of *Medhya rasayana,* [consisting of *Mandukaparni* (*Centella asiatica* Linn.)*, Guduchi*, *Yashtimadhu* (*Glycyrrhiza glabra* Linn.)*,* and *Shankhapushpi* (*Convolvulus pluricaulis* Choisy), milk powder, and sugar powder] and yoga intervention on the short-term memory of the subjects. The short-term memory was assessed using two tests (1) short-term memory test pictures and (2) serial recall effects test using memory scope. A significant difference and an improved memory among subjects treated with the *Medhya rasayana* was found. No adverse events were observed during the study period. [111]

A randomized double-blind placebo-controlled clinical trial to study the effect of Livwin (a polyherbal formulation) on 60 patients with acute viral hepatitis was conducted. It was concluded that the formulation resulted in a significant early recovery in patients without complications. Also, the biochemical tests showed recovery of levels of serum bilirubin, Aspartate Transaminase (AST) and Alanine Transaminase (ALT) which were earlier increased in the treatment group. However, 10.37% of the subjects reported epigastric pain and diarrhea during the course of study. [112]

No toxicity was reported while using Ayurvedic interventions containing Guduchi (TC) in COVID-19 patients even when used along with standard care treatment. Ayurvedic medicines have shown to reduce the time to symptomatic recovery in asymptomatic and mildly symptomatic COVID-19 patients. [113,114]

Hepatoprotective, neuroprotective, anti-diabetic, and radioprotective effects

The beneficial effects of aqueous extract of *T. cordifolia* have also been observed in the management of chronic alcoholism. Significant reductions in the urine biomarkers were reported by *Mittal et al* in their study in which 100 ml of freshly prepared aqueous extract of *Tinospora cordifolia* was administered in patients with chronic alcohol consumption. [91] A similar study to determine the effects of *T. cordifolia* administration on patients with chronic and moderate alcoholism was conducted by *Sharma et al.* The authors concluded

that treatment with *T. cordifolia* effectively increased intestinal absorption of vitamins and helped in improving the retaining power of the liver that regulated the alcohol-induced multivitamin deficiency. Vitamin metabolism biomarkers, i.e. homocysteine and xanthurenic acid, were also normalized after intervention. [115]

Singh et al. in their clinical study highlighted the use of the aqueous extract of *T. cordifolia* (500mg dose twice in a day for 6 months) as an adjunct treatment with chloroquine base for the treatment of hyper-reactive malarious splenomegaly. The authors concluded in their study that the addition of *T. cordifolia* along with chloroquine reduced the regression of the spleen by 37-50% in the first six weeks. Further, there was a regression of 45-69% after the end of six months from the initiation of treatment. The authors also found a decrease in IgM values and an increase in hemoglobin and well-being (assessed by the Karnofsky performance scale). [116]

In a clinical trial conducted on active TB patients,undergoing anti-tuberculous treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, where *Curcuma longa* and *Tinospora cordifolia* were given as herbal adjuvant. The herbal adjuvant group was found to have reduce hepatotoxicity significantly and improved patient compliance without any side effects . [117]

In a single-blind controlled study by *Vyas et al.,* the authors studied the effect of *Rasayana* drugs (*Amalaki - Emblica officinalis Gaertn., Guduchi - Tinospora cordifolia willd., Ashwagandha - Withania somnifera L. Dunal, Yastimadhu - Glycyrrhiza glabra Linn., Pippali - Piper longum Linn., Sariva - Hemidesmus indicus R.Br., Kustha - Saussurea lappa Falc., Haridra - Curcuma longa Linn. and Kulinjan - Alpinia galangal Linn*.) as an adjuvant therapy with anti-Koch's treatment in 133 patients. The adjunct therapy enhanced better physical and mental well-being in the patients. No adverse events during the course of treatment were observed. The authors finally concluded that the *Rasayana* therapy has an antioxidant effect, acts as an immunomodulator, and also has nutritive value. [118]

Study have also documented the role of Giloy in gingivitis. This clinico-microbiological study concluded that twice rinsing of *T. cordifolia* decoction as a mouth rinse in adjunct to scaling and routine brushing of teeth for 21 days showed anti-plaque, anti-gingivitis, and antimicrobial action against gram-negative organisms and *S. mutans*. [119]

Sharma et al in their study collected information on the use of various traditional plants for the treatment of jaundice by 91 traditional healers in the sub-Himalayan regions of Uttarakhand state In India. The authors used structured questionnaires and personal interviews to collect the information. The authors concluded that a total of 40 medicinal plants (of which *T. cordifolia* was one) were identified that were used for the treatment of jaundice in that region. [120]

Aqueous extract of *T. cordifolia* may be used to alleviate the toxic effects of alcohol and to modulate testosterone and cholesterol biosynthesis. [121]

A randomized controlled trial done in patients with diabetes mellitus found that *T. cordifolia* treatment can reduce blood glucose levels as well as lipid levels in these patients. [122]

In an open-label, prospective study conducted by CCRAS, Ministry of Ayush, the effect of *Gokshuradi Guggulu* (1 gm twice daily) and *Guduchi Churna* (3 gm twice daily) for 84 days was evaluated on type II Diabetes mellitus (DM). A significant reduction was observed in the symptoms of diabetes (assessed in DSQ score). The study reveals that the selected management has the potential to reduce symptoms of type 2 DM and revealed the clinical safety of trial interventions. [123]

Sharma et al. demonstrated the combined effect of Ayurveda intervention, yoga, and lifestyle modification in pre-diabetic and diabetes type 2. Along with allopathic treatment, ayurvedic treatment with *Mamajjaka Churna, Amalaki Churna, and Guduchi Churna* two times/day was administered to **7735** participants. Along with treatment protocol for disease management, lifestyle modification with *Yogasana* was suggested. The authors of the study concluded that the Ayurveda treatment and the *Yogasana* practice in conjunction with the allopathic treatment were helpful in the management of diabetes. No adverse events were reported in the study. [124]

Another study evaluated the safety and efficacy of *Amruta Bhallataka* (has *Tinospora cordifolia* as the main ingredient) in Osteoarthritis (OA) in comparison with Glucosamine sulphate (GS). It was found that *Amruta Bhallataka* had significant activity in OA. However, an asymptomatic reversible rise in liver enzymes was noted in the *Amruta Bhallataka* group, but without any serious adverse events. [125]

Chopra et al. conducted an investigator blind, randomized parallel efficacy, 4-arm multicenter drug trial in 92 patients to evaluate the safety of higher doses of *Shunthi - Guduchi* formulations in the treatment of osteoarthritis - Knee. Formulations prepared from *Shunthi, Guduchi, Amalaki, Bhallataka parpati* and *Shallaki guggulu* were administered. The authors found that despite an increase in the optimum doses and over and above the doses used in earlier trials, the combination of *Shunthi – Guduchi* along with *Bhallataka parpati* and *Shallaki guggulu* improved the efficacy (pain relief) without increasing the adverse event profile. [126]

A study of *Banerjee et al*. demonstrated the antioxidant activity of the leaf of *T. cordifolia* in Chikungunya patients with persistent polyarthralgia. The authors concluded that the herb possesses antioxidant activity as it significantly scavenged the intracellular Reactive Oxygen Species (ROS). No adverse events were observed in this study. [127]

Chopra et al. conducted a randomized, double-blind, controlled equivalence drug trial to understand the efficacy of a polyherbal formulation (containing *Tinospora cordifolia, Zingiber officinale, Emblica officinalis, Boswellia serrata*) in the treatment of symptomatic knee osteoarthritis. The equivalence of the formulation was assessed with celecoxib and glucosamine. A total of 440 subjects participated in the study. The authors concluded from their study that the polyherbal formulation was effective in significantly reducing knee pain and helped in improving knee function. The authors also concluded that the effects of the formulation were equivalent to the effects of celecoxib and glucosamine. However, in this study, 20 subjects in the ayurvedic intervention group had an asymptomatic increase in the Serum Glutamic Pyruvic Transaminase (SGPT). The liver function levels were otherwise normal. [128]

The efficacy of *T. cordifolia* containing ayurvedic treatment in rheumatoid arthritis was demonstrated by Chopra et al. The treatment showed comparable efficacy as compared to Hydroxy-chloroquine (HCQ) without any serious adverse events. [129]

No adverse effects of treatment with plant extract was seen on haematological biochemical parameters of the patients participated in another clinical trial with Amrita ghrita on Rheumatoid arthitits (Amavata). [130]

Peterson et al. in their study assessed the metabolic interactions and prebiotic potential of medicinal herbs that have been used in neuro-degenerative diseases and as nootropics. The medicinal herbs were *Kapikacchu, Gotu Kola, Bacopa/Brahmi, Shankhapushpi, Boswelia Frankincense, Jatamansi, Bhringaraj, Guduchi, Ashwagandha or Shatavari.* The study concluded that the gut microbiota is involved in both protein and glycan catabolism and provided the amino acids and the sugar substrates that are used by fermentative species. Herb-induced microbial communities are predicted to alter the relative abundance of taxa encoding SCFA (butyrate and propionate) pathways. Co-occurrence network analyses identified a large number of taxa pairs in medicinal herb cultures. Some of these pairs displayed related culture growth relationships in replicate cultures highlighting potential functional interactions among medicinal herb-induced taxa. [131]

Covid-19 clinical trials

In an exploratory, non-randomized study, impact of *Guduchi* and *Pippali* decoction (in a dose of 100 ml) was studied as an add on to the standard of care treatment in mild to moderate cases of Covid 19. The outcomes were evaluated in terms of the duration of hospital stay, the time to clinical recovery, safety, and non-interference/interaction of Ayurvedic medication. It was observed that the decoction reduced the hospital stay and improved the recovery period better than the Standard of Care treatment group. [114]

In an open-label pilot study, the outcomes of *Guduchi Ghana Vati* in a dose of 500 mg twice daily in 15 participants for ten days were compared with the outcomes of Hydroxychloroquine (control) in asymptomatic to mild cases of COVID-19 infection. It was observed that *Guduchi Ghana Vati* exhibited a lowering of time to RT-PCR negative status as compared to control group. [132]

The effect of *Guduchi Ghana Vati* was studied in prevention of COVID -19 in containment zones of Hamirpur, Himachal Pradesh by CCRAS, Ministry of Ayush. Total 1165 participants (aged 18- 60 years) received *Guduchi Ghana Vati* in a dose of 500 mg on empty stomach for 30 days. It was observed that the incidences of Covid positive cases was only 0.1%. *Guduchi Ghana vati* was found to be safe and effective as a prophylactic measure in preventing the infection. [133]

A recently conducted randomized controlled trial demonstrated that ayurvedic treatment containing Giloy can expedite virological clearance, help in faster recovery and concomitantly reduce the risk of viral dissemination. It can also reduce inflammatory markers thus reducing the severity of SARS-CoV-2 infection. Moreover, there was no adverse effect observed to be associated with this treatment. [134]

CRITICAL EVALUATION AND COMPREHENSIVE REBUTTAL OF RESEARCH PUBLICATIONS By Nagral *et al* (2021) and Kulkarni *et al* (2022)

Background

Recently, two research articles by Indian researchers on hepato-toxicity of *Tinospora cordifolia* by Nagral et al. (2021) [56] and Kulkarni et al. (2022) [58] were published. They made more media headlines, rather than academics creating a lot of confusion, not only in the mind of the lay public, but also among the practitioners of Traditional Systems of Medicine including experts of Ayurveda, Siddha, and Folklore Medicine.

COVID- 19 struck the world, like a thunderbolt. There was no specific treatment for this viral disease, which appeared on the planet for the first time. No therapy from any system of medicine - modern, AYUSH or any other alternate/ancient herbal-based therapy was available. Herbal products, which have been used for the millennia for general well-being and their role in improving general immunity found their way into popular uses. They were not only promoted by AYUSH practitioners but the public at large being familiar with these drugs started using them for the fear of this new unknown killer disease. Even folklore knowledge promoted the use of these medicines.

The onset of the Covid-19 pandemic pushed the demand for Ayurveda products in India. The interest in these products was mostly been fuelled by the recommendations from the Ministry of Ayush to fight the Coronavirus. In the last quarter of 2020, many companies, large and small, have witnessed growth between 50-90 percent. Market Research Company, Nielsen's report in July revealed that *Chyawanprash* sales have increased by 283 percent and the sales of branded honey increased by 39 percent during the pandemic period. The rising sales were also registered by Indian Medicines Pharmaceuticals Corporation Limited (IMPCL), a government enterprise and manufacturer of Ayurveda and Unani medicines. [135] During the period of pandemic, many herbal products including Guduchi were increasingly being used by the masses, all over. We critically analyse these two publications, here, which categorically concluded Guduchi to be a hepato-toxic herb.

Nagral et al. 2021

Tinospora cordifolia was used as an immune booster for prophylaxis against COVID-19 in this study. Six patients with a median age of 51 years (range 38-62) with a history of *T. cordifolia* consumption, presented with symptoms of acute hepatitis during the study period of 4 months during the COVID-19 pandemic. Median duration of consumption (IQR) was 90 days with a range of 21-210 days. Four of these 6 patients (all females) had underlying silent chronic liver disease of possible autoimmune etiology associated with other autoimmune diseases, like, hypothyroidism and Type-2 Diabetes mellitus. All the patients presented with acute hepatitis and recent exposure to ingestion/ consumption of a distinctive formulation containing TC, as reported by the authors.

Broader issues with the study of Nagral et al. (2021)

1. In this observational hospital-based study, 6 patients with liver injury were evaluated for the possible cause of injury due to the herbal drug, *Tinospora cordifolia* which was taken in various forms without any understanding of the amount, and dose, quality, and impurities.

2. The first patient in this series of six patients used *Tinospora cordifolia* with Cinnamon and Cloves. How can *Tinospora cordifolia* alone be held responsible for liver damage?

3. The first patient consumed 10 to 20 pieces of twigs of *Tinospora cordifolia*. The properties of a consumed herb like thickness, circumference, length, and even species of *Tinospora* were not known (there are 34 species of *Tinospora*). The second patient consumed one twig of *Tinospora cordifolia*, which was boiled and extract consumed. In case of the third patient, 3-4 *Tinospora cordifolia* twigs were boiled and 5ml extract per day was consumed. Thus, the details are insufficient to understand the posology and toxic nature of the herb.

4. The fourth patient was an elderly with pre-existing diabetes mellitus who developed ascites because of cirrhosis/fibrosis of the liver following consumption of commercially available *Tinospora cordifolia* syrup. No details of the commercial preparation, dose, or other aspects of posology were available. The fifth patient gave a short, 3 weeks history of consumption of *Tinospora cordifolia* plant-boiled extract of 1 twig, 2-3 days per week. The patient developed autoimmune hepatitis, with cirrhosis and ascites in a short duration of 3 weeks of consumption of *Tinospora cordifolia*. This appears unlikely. COVID-19 per se has been reported to cause autoimmune hepatitis. The sixth patient, a 56-year-old female with hypothyroidism, who presented with jaundice of 20 days duration with a history of consumption of commercially available pills (one per day) of *Tinospora cordifolia* for 3 months before she developed liver damage. The nature of *Tinospora cordifolia* pills, source, composition, and posology remained unclear.

5. In a maximum number of the reported cases, adequate laboratory work-up was not undertaken. For example, in the second patient, the initial serum bilirubin was 15.3 mg/ dl (direct bilirubin 10.9 mg/dl). It is not sure whether any clinical investigation was undertaken to unravel the cause of elevated indirect bilirubin (4.4 mg/L). In third patient, at presentation total serum bilirubin was 20 mg/dL (direct serum bilirubin 10.7 mg/dL and indirect serum bilirubin 9.3 mg/dL). An existing B-Thalassemia minor can very well explain markedly elevated indirect serum bilirubin. Possible history of repeated blood transfusion and other medications have not been considered. In the fourth patient, serum bilirubin continued to rise despite the stoppage of *Tinospora cordifolia* intake at the time of hospitalization. In some patients, antinuclear antibodies, smooth muscle antibodies, and serum immunoglobulins all were normal but diagnosis of autoimmune hepatitis was considered. It is unlikely that the usage of herbal products can be held responsible. *Tinospora cordifolia* has been used by millions of healthy individuals over hundreds of years without any side-effect, in fact, in the classical Ayurvedic literature, Giloy is described as a hepato-protectant[97], which is also supported by research evidences stated in section above.

6. No expert of Ayurveda was involved in the study, which is a requirement when an Ayurvedic preparation is being evaluated on human subjects. It is the responsibility of the Institutional Ethics Committee to follow the tenets of "Ethical considerations in the biomedical research on Human subject" (Para 7.13 from the 2017 guidelines of ICMR, New Delhi) [136].

7. The first patient presented with a fifteen-day history of jaundice with a total bilirubin of 7.9 mg/dl. *Tinospora cordifolia* (and cinnamon and cloves also) must have been stopped in the hospital if they were suspected to have caused liver injury. It is a matter of scientific inquiry, that what led to the peak serum bilirubin level of 45.1 mg % during the hospital stay. Total leucocyte count was elevated at the time of presentation (16,000 cells/cmm), for which reasons remained unexplored. All possible causes of leukocytosis like infections, toxins, or any other cause should have been investigated. Authors should have disclosed the details of the administration of antibiotics if any. Could we think of the possibility of antibiotics causing liver damage or worsening liver functions after hospitalization? Many more such details related to patients in uncontrolled clinical case reports may unravel many more possibilities.

8. During 4 months of the study period from September - to December 2020, several thousands of patients may have developed acute hepatitis and many thousands may have consumed *Tinospora cordifolia*, and certainly many may not have used *Tinospora cordifolia* in any form. Many drugs that were used in the treatment during a hospital stay may cause hepatic injury. Many COVID 19 cases remained undetected and infection, if it was there and remained undetected, may have caused liver damage. A meticulous workup for COVID 19 is a cumbersome process. RT PCR, the gold standard of the COVID-19 test has only a 70-80% detection rate. In this study, wherever a history of *Tinospora cordifolia* use was reported, it was concluded to be the cause of liver damage. But what about those, who had never consumed *Tinospora cordifolia*? In such cases, it is logical to attribute it to other co-morbid conditions which were present in the form of diabetes mellitus and hypothyroidism. It seems to be a selective reporting to attributes to the use of *Tinospora cordifolia* as the cause of liver damage in all reported cases.

9. Viral markers in the form of hepatitis A, B, C, and E, were undertaken by serological tests. It is a well-known fact that Epstein-Barr virus and cytomegalovirus infection may also cause liver damage. They have not been excluded. Many other possible causes of hepatic injury were not been excluded, at least it has not been deliberated.

10. Authors, themselves, have accepted that "patients underwent a liver biopsy to assess the severity of the liver injury and determine the likely etiology". However, the biopsy findings as have been reported in the paper, cannot be conclusive evidence of liver injury caused by *Tinospora cordifolia*.

11. Authors have further reported that in their case series, 4 patients had features of pre-existing chronic liver disease (CLD) with features of auto immure hepatitis, on liver biopsy. All these four also had additional autoimmune diseases (two had diabetes mellitus and 2 had hypothyroidism). Three of the four had positive auto-immune markers and one had significantly high IgG. Out of two patients without evidence of chronicity, one had antinuclear antibody positivity and the other had interface hepatitis with plasma cells and eosinophils. It is difficult to understand, why the authors concluded that all these patients were cases of liver damage caused by *Tinospora cordifolia* usage.

12. Authors noted that four out of six patients consumed boiled extracts of *Tinospora cordifolia* twigs, while one patient used a commercially available pill formulation and another one consumed it in the form of commercially available syrup. All of them had self-prescribed *Tinospora cordifolia* formulation without supervision of a qualified AYUSH physician. Without the involvement of a qualified AYUSH expert, the whole sanctity of the conclusion comes under scrutiny. It is not logical to conclude, based on the foregoing that use of *Tinospora cordifolia* was harmful to the liver. It will not be out of place to mention that *Tinospora cordifolia* has been used for its beneficial effects on the liver for centuries with lab studies also supporting for a beneficial effect on liver.

    It is a common practice to stop an alleged drug when drug-induced toxicity is encountered. Discontinuation of a harmful drug generally leads to the reversal of harmful effects. In this study, despite the discontinuation of *Tinospora cordifolia* in many patients, liver damage continued to progress. In fact, one patient died during the tapering of corticosteroids. One of the earlier published works also found a similar outcome.

Other limitations of study:

1. The updated Roussel Uclaf Causality Assessment Method (RUCAM) score showed **possible** drug-induced liver injury (DILI) in 4 and **probable** drug Induced liver Injury in 2 patients. The level of certainty that *Tinospora cordifolia* may have caused the liver damage is low, and it cannot be concluded to be the cause of liver injury.

2. The alkaline phosphatase rise was minimal in all patients and none of the patients had any coagulopathy.

3. Authors themselves have reported immune-protective effect of *Tinospora cordifolia* that improved surgical outcomes of patients with obstructive jaundice. [137]

4. Authors have further revealed that there have been no reports in the literature of *Tinospora cordifolia*-related injury to the liver, barring one isolated case of acute hepatocellular injury due to the use of *Tinospora cordifolia* from USA. [57] An account of 3 patients with acute hepatocellular injury and jaundice after taking ayurvedic supplements was reported by Karousatos. Only one patient had taken *Giloy kwatha* (decoction of *Tinospora*) and the other two were on some other herbal medications. The patient who consumed Giloy kwatha was a 68 years old female with a history of hypothyroidism, dyslipidaemia and borderline diabetes mellitus. She stopped Giloy a week after the development of jaundice. Within one month of stopping this drug, her liver functions became normal and remained normal later. This patient was taking *Giloy kwatha* to improve her overall health. Four months later, the routine investigations revealed acute hepatocellular injury. Liver biopsy was not performed in this patient. The RUCAM score was **probable.** Authors themselves concluded that, there is nothing specific that can implicate *Tinospora* as the cause of liver damage. Karousatos *et al* have noted that *Tinospora crispa*, a different species of *Tinospora is* known to be hepato-toxic. Thus, while evaluating toxicity related to ayurvedic and/or other herbal supplements, raw material identity, quality and dosing are the real challenges. Authors have also opined that the observations represent a shared association with liver injury in ayurvedic medicine and there will always be inherent limitations while correlating a specific herb to be the cause of acute liver injury.

5. This herb has been found to be effective in HIV, which primarily affects the immune system. Thus, it is unlikely that the herb could harm the liver by an autoimmune mechanism. The auto-immune nature of liver injury remained unsubstantiated following *Tinospora cordifolia* use. *T. cordifolia* has also been noted to increase IgG antibody titer with enhanced macrophage activation. Immune boosting potential of *T. cordifolia* helping in HIV infected patients is well reported. [138] Syringin, cordiol, cordioside and cordiofoliosides-A and cordiofoliosides-B are the active ingredients of *T. cordifolia* responsible for its immune stimulant activities. [139,140] Thus, *T. cordifolia* usage cannot lead to the progression of pre-existing liver disease as well. It seems very far-fetched to infer that the use of the immune stimulant effect of *T cordifolia* could have exacerbated an underlying liver disease.

Kulkarni et al (2022):

Kulkarni et al, 2022 reported a retrospective multicenter study spanning 13 centers. The study was designed to identify features of Giloy-induced liver injury. They observed that usage of Giloy is associated with auto-immune hepatitis.

We have strong reservations against their observations, as follows:

1. It is a retrospective study with all the limitations of such a study design.
2. Study comprised of 43 subjects spanning over 13 centers at 9 geographical locations in India. It is not sure whether all the ethical considerations of biomedical research on human subjects were complied to or not and necessary ethical approvals were considered or not?
3. Authors have noted that only 25 patients, out of a total of 43 had consumed Giloy in pure/extracted form. Rest other 18 had ingested multi herbal formulations. Whereas, the title of the research paper reads "*Tinospora cordifolia* - induced liver injury during the covid -19 pandemic", as if all the liver injury were related to *Tinospora cordifolia* alone. The title also reads "liver injury during the COVID-19 Pandemic". However, there is nothing to do with COVID-19 in this study, except for the study was undertaken when COVID-19 was rampaging throughout the country. The study period extended from April 2020 to July 2021. COVID-19 vaccines were launched in the country in January 2021, but the status of COVID-19 vaccination of these patients was not furnished.
4. During the study period of 16 months, these 13 tertiary centers which participated in the study might have seen many more patients with liver disease. The details of these patients might have brought out some additional valuable information. Many patients with existing liver disease might have consumed Giloy during the pandemic as an Ayurvedic supplement. In this study, seven patients had pre-existing chronic liver disease from among the 17 who had acute hepatitis.
5. Authors reported that "several other supplements such as Aloe Vera, Indian gooseberry and turmeric were consumed by the patients intermittently during the time period of Giloy consumption which are also potentially (synergistically) hepatotoxic". These three herbals, are

considered to be safe for human health with many beneficial effects. Indian gooseberry is known as '*Dhatri Phala'* (fruit which is similar to mother), inferring that, the fruit can never harm. Turmeric is one of the most important herbal products that is being used all over the country for millennia. Many curcuminoids, like- curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin, volatile oils like- turmerone, atlantone and zingiberene, and many more are being patented for their medicinal properties. Thus, the statement of the authors is unjustifiable.

6. It would have been worthy to analyse all the patients with chronic liver disease, acute liver failure (ALF) and acute-on-chronic liver patients, who came to these 13 tertiary centers during the period under review. Selecting a mere sample with a history of consumption of a specific herb and inferring the observations is not arguable.

7. For herbal medicines, the extension of the CONSORT statement need details of the key characteristics of the product that has been used when conducting a randomized controlled trial (RCT). Only a total description may be allowed to determine the safety/efficacy of the product. Given the retrospective nature of the study, the safety of the herbal product in question cannot be conclusively determined. It would have been worthwhile to verify the claims using an RCT design following the CONSORT guidelines.

8. The question arises about the lakhs of patients, who suffered from liver disease during these 16 months of the COVID pandemic and who had never taken 'Giloy'. According to World Health Ranking (worldlifeexpectancy.com) published in 2018, liver disease deaths in India reached 264,193 or 3% of total deaths during the pre-COVID period. A similar trend might have continued during the COVID-19 pandemic. A detailed audit of all these deaths will provide more insight into the causes and pathogenesis. Selective reporting of few patients of liver disease based merely on presumed association is not a well-founded scientific inquiry.

   To put this discussion on Giloy and liver injury in proper perspective, the scenario of renal disease in India can be briefly discussed. Chronic kidney disease (CKD) is a very common problem in our country. According to Singh et al (2013), the prevalence of CKD was observed to be 17.2% with approximately 6% having CKD stage 3 or worse in the adult population. Hypertension, diabetes mellitus, and anemia were the most common risk factors in this study. It was a large, community-based cross-sectional study. [141] However, it is a very common observation in the setting of primary health care set up to find patients with deranged renal function with or without known risk factors. If a primary physician finds a history of herbal drugs being taken by the patient with CKD for any length of time or amount. Then without going into the detail of which drug was taken, herbal preparation is very conveniently labelled as a cause of CKD.

   Authors have reported that "Our findings support the previously described clinical, investigational and histological features associated with *Giloy* induced liver injury". However, they have not enlisted any study to support this statement. Elsewhere, they have quoted the Nagral *et al* study (2021) in support of their observation, that "*Giloy*- related hepatitis appears to be associated, both with herb-induced autoimmune hepatitis or herb-induced liver injury with autoimmune

hepatitis features and a flare of chronic autoimmune hepatitis due to Giloy's immune potentiating properties". The above statement of Kulkarni *et al* (2022) is based on the observation on 43 patients, and out of which only 25 had taken *Giloy* as the lone herbal supplement, rest consumed polyherbal preparations. This is an absolutely misplaced observation with bias against *Giloy.*

Even during the Giloy consumption, 5 patients (11.6%) intermittently consumed other herbal formulations. These included Aloe vera and Indian gooseberry (Amla) decoction; the classical Ayurveda formulation Arjunarishta; a polyherbal proprietary drug containing Giloy as active ingredient; turmeric (*Curcuma longa*) and Tulasi (*Ocimum sanctum*); and pepper, ginger and clove extracts in one patient each (2.3%). Thus, evaluating toxicity related to ayurvedic and/or other herbal supplements becomes a challenge.

9. Authors have presented their observations and said that the development of hepato-toxic symptoms start from 2 to 365 days after the consumption of Giloy-based formulation. This is very interesting. The authors concluded that someone developed liver injury within 2 days after the Giloy use. That too for an herb that has been reported to be hepatoprotective in classical literature and modern research publications.

10. The authors have recorded that "a total of six different types of Giloy formulations were retrieved from the patients which underwent chemical and toxicological analysis. They analyzed raw herbs and drug samples retrieved and they found differential (quantitative) presence of potentially hepatotoxic phytochemicals such as terpenoids and plant alkaloids while trying to rule out other known hepato-toxic components, such as impurities and contaminants. These samples included fresh Giloy plant retrieved by the patient, privately pharmaceutical manufactured Giloy decoction, locally available and publicly sponsored state pharmacy manufactured product by private Ayurvedic companies.

11. Heavy metal contamination with mercury, arsenic, lead and cadmium, over and above prescribed limits, were noted in two samples. Gas chromatography analysis revealed multiple photochemical with potential immune-modulatory effects and hepatotoxic potential. Gas chromatography analysis revealed chemicals such as sesquiterpenes, diterpenoids, glycosides and phytosterols. Some samples also found industrial solvents, presumably introduced inadvertently during the manufacturing process.

    GC/MS-MS scan found many harmful organic and inorganic compounds in the various samples that were analyzed. Many phenolic compounds, nitrosamines cobalt hexahydrate, nitosomethane, paromomycin, benzophenone, chromium hydrate, lithium chloride, chromium hydrate etc. were also found. Their contribution to liver injury has not been elucidated.

    The above contaminants may have been the actual cause of the hepatic injury seen in some patients

12. The main concerns about the herbal drug are:

- *Fresh Giloy plant submitted for analysis may not have been the same plant source as was consumed by the patient.*
- *For any research study to be credible, we must have quality control of the product being used. In this study, we can't be sure of the actual plant being Tinospora cordifolia or not. There are 34 species of Tinospora available with quite similar morphology and only an expert of Ayurveda or herbal expert can differentiate.*
- *Even the quality of the product being taken from various private sources as described by the authors is not guaranteed to be a quality product as has been admitted by the authors themselves. Further details of such products are not provided in the publication.*
- Many fungal species are normally found to be endophytic with Tinospora cordifolia. Such endophytic fungi may contain toxins that can contribute to liver injury. Without taking this into account, we can't reach to a conclusion on safety and efficacy of Tinospora cordifolia.[142]

13. Twenty-two patients underwent a biopsy in this study. According to RUCAM score, Giloy-induced liver injury was "possible" (score 3-5) in 9 patients (40.9%) and "probable" (score 6-8) in 13 patients (59.1%).

    During the follow-up period of these 22 biopsied patients, new or worsening clinical events were seen in 15 patients as follows- ascites in 2 (9.1%), hepatic encephalopathy in 3 (13.6%), and sepsis with a portal hypertension event in 1 (4.5%). Clinically, it has been observed in practice for the resolution or stabilization of most of the drug-induced changes, when the offending agent is withdrawn, if permanent damage to the organ system has not taken place. In this study, 15 of the 22 patients continued with the worsening clinical condition. It calls for the investigation of other causes of liver injury. Considering such results, it is not logical to conclude unequivocal conclusion of the research paper "Tinospora cordifolia (Giloy)- induced liver injury…"

14. Drug samples were analyzed only in a few patients. It is not certain that representative samples were being submitted for analysis. It is also not sure about the quality of the drug, in a situation, where the raw herbs or privately unregistered manufacturers supplied the preparations. In standard clinical studies, aspects including quality and uniformity of drug sample, source and batch etc. are extremely important.

15. Out of 34 species of *Tinospora*, Ayurveda recommends the use of only *Tinospora cordifolia* (*Guduchi* or Giloy) for the healthful benefits. During the course of the pandemic, other species of *Tinospora* might have been used by a few, considering the plant as *T. cordifolia*. This cannot be denied in the current study as well.

16. Authors have analyzed patients suffering from liver injury who visited tertiary care hospitals for their treatment. Many of the patients in this study were also using many other herbal preparations apart from Giloy. But all the patients suffering from liver injury in this study, are being concluded to be caused by Giloy use if it was a component of the herbal preparation being used. This is not a well-founded conclusion.

17. Authors have themselves identified several limitations of their study, as below:

    - *It was a retrospective study, meaning thereby that "some clinical and investigational data are incomplete".*
    - *Treatments were heterogeneous, which could have affected the outcome.*
    - *Authors affirmed that their data collection methods were designed to include the minimal diagnostic elements required to substantiate the diagnosis of the idiosyncratic Drug-Induced liver injury (DILI) and herb-induced liver injury (HILI).*
    - *All patients had negative hepatitis C virus antibody, but a hepatitis C RNA polymerase chain reaction test was not performed at all.*
    - *They admitted that they were not able to clarify liver toxicity due to mislabeled and undisclosed ingredients in multi-herbal products containing Giloy.*
    - *The exact component(s) that caused liver injury with multi-herbal products containing Giloy use was unknown.*
    - *A direct dose measurement of Giloy or Giloy-based formulations taken by patients could not be recorded, as many samples were unlabeled, and also raw herbs were used to make extracts at home.*
    - *The recorded dose of each patient was an estimate with the possibility of recall bias, and a realistic toxic dose calculation could not be performed.*
    - *Authors have noted that several other supplements were intermittently consumed during the time period of Giloy consumption, such as aloe vera, Indian gooseberry, and turmeric which were also potentially (synergistically) hepatotoxic.* This statement is also not based on the facts.
    - *Only half of the patients consented to liver biopsy, so histological assessment for classical Autoimmune Hepatitis (AIH) was not possible in every patient. They further stated that "most of the available biopsy samples did not display histopathological features of classical AIH, and the pretreatment revised AIH scores among biopsied patients were not suggestive of definite AIH in any". However, they concluded in the same breath that "Atypical features such as the portal-based, mixed pattern of inflammation associated with cholestasis were predominant, demonstrating a high* ***probability*** *of herb-induced hepatitis with autoimmune features due to Giloy use*". How their final conclusion was drawn, is difficult to comprehend.

- ❖ *The RUCAM scores indicated that all the patients were in the **possible** or **probable** range for liver injury associated with the consumption of herbal medicines.*
- ❖ *Authors quoted the observations of Hunt et al [143] that "many patients developed features of severe injury on 1st exposure, which improved after herb withdrawal"; whereas, out of 22 biopsied patients in this study, 15 patients continued to worsen clinically during the hospital stay. The current observations are not matching with the observations of cited work.*
- ❖ *Serologies for rare viral infections such as cytomegalovirus and Epstein Barr virus were not performed.*
- ❖ *Authors have argued that the "samples might have been contaminated with Tinospora crispa, a related species with known hepato-toxic potential due to the presence of clerodane furano-diterpenoids". [144] Thus, in such doubtful situations, one cannot label T. cordifolia with toxic nature.*

18. Based on such a flawed research study, it is not appropriate to draw a sweeping conclusion that all patients had *Tinospora cardifolia (Giloy*) induced liver injury in this study.

Furthermore, as claimed by the authors themselves many patients in their cohort were suffering from co-morbid conditions, like- close to one-third of patients were diabetic, nearly half were obese, three-fifth required in-hospital management and a quarter required intensive care. All these conditions are well recognized to be associated with non-alcoholic steatohepatitis thus leading to clinical hepatitis. [145] Combining the data from the two studies, we found that 30 patients out of 49 showed positive results on autoimmune profile testing, the authors have hypothesized that Giloy may have unmasked autoimmune hepatitis in such cases. We would like to highlight that etiology of autoimmune hepatitis is not clear, interaction of genetic as well as environmental factors are thought to be likely involved. [146] The authors themselves have reported that some patients in their cohort were having thyroid disorders and Sjogren's syndrome, these conditions are known to be associated with autoimmune hepatitis. The authors have applied the Roussel Uclaf Causality Assessment Method (RUCAM) to ascertain the causality with Giloy, but we would again like to highlight that RUCAM score of none of their patients was more than 8, thus none of their patients was having a definite drug-induced liver injury. Kulkarni et al have themselves mentioned that their patients were having scores compatible with only possible or probable drug-induced liver injury. We would also like to assert that the RUCAM scale is not the gold standard for the diagnosis of drug-induced liver injury and this scale has its own shortcomings, like- low intra- and inter-rater agreement. [147]

With the foregoing statistics of liver disease in the population, 6 patients of liver injury reported by Nagral et al. in their study and majority of them with co-morbidities; and 43 similar patients from 13 tertiary centers by Kulkarni et al. and majority again with co-morbidities have been concluded that administration of a herbal drug (Giloy) alone or in combination with other herbal preparations to be the cause of liver disease and death. This conclusion seems to be not based on the scientific facts reported in these two research publications. Administration of this herb alone or in combination in such patients, at the most, may be hypothesized to be investigated for possible hepatotoxicity.

CONCLUSION

Tinospora cordifolia (Willd.) Miers (Menispermaceae) is an herbaceous vine indigenous to the tropical areas of India, Myanmar, and Sri Lanka. In vernacular, it is known as amrita, Guduchi. The Ayurveda literature contains about 2400 Ayurveda formulations in more than 24 dosage forms with *Guduchi* as an ingredient. These formulations are widely used through different routes of administration for more than 95 pathological conditions. It is said to be the best *Rasayana*. A special focus has been made on its health benefits in treating various disorders and its potential as an immune booster and aiding in the betterment of human life expectancy. Its versatile use in multiple clinical conditions and in various dosage forms, through multiple routes of administration, justifies its synonym *Bhishagpriya* (~favored by physicians).

Medicinal applications in countering various disorders and its usages as anti-oxidant, anti-hyperglycemic, anti-hyperlipidemic, hepato-protective, cardiovascular protective, neuro-protective, osteo-protective, radio-protective, anti-anxiety, adaptogenic, analgesic, anti-inflammatory, anti-pyretic, anti-diarrheal, anti-ulcer, anti-microbial, and anti-cancer etc. have been established and reported. In the Ayurvedic as well as other Indian medical systems literature, there are several uses of *Guduchi* described and it has been successfully used in clinical practice. It is used as a major component of therapeutics for ameliorating metabolic, endocrinal, and several other ailments, aiding in the betterment of human life expectancy.

As regards toxicity evaluation, there are studies done on pre-clinical models as well as clinical phase I and II. Publications from such studies provide evidence for its safety and efficacy. Many studies have reported its anti-toxic nature. It has been well demonstrated that *Guduchi* does not exert any remarkable adverse effects on the cardiovascular system, renal system, central nervous system, and gastrointestinal system. Comparative efficacies of TC with conventional treatment have been also evaluated (e.g. in osteoarthritis) OR as adjuvant with conventional treatment. (e.g. with Anti Koch's treatment as hepatoprotective agent). In either of them, no remarkable adverse effects are reported. Administration of T. cordifolia to healthy volunteers has also been found to be safe as shown in many studies.

During the COVID-19 pandemic, it has been widely used as a medicine for prevention as well as therapeutic management. Its intervention has reduced the length of hospital stay and improved the recovery time in mild to moderate COVID-19 cases. A general feeling of well-being and activity levels was also reported to be better in a three-month follow-up study. Considering the multi-variant activities; the Interdisciplinary Committee for integration of Ayurveda and Yoga Interventions in the 'National Clinical Management Protocol: COVID-19' has recommended the use of TC in COVID-19. The herb has been used across the country by lakhs of healthy and COVID-positive individuals, where no such toxic manifestations were noticed that can convincingly prove the harmful nature of this plant.

The safety of TC can be inferred from the efficacy-related clinical studies where no adverse effects are reported. The data on its widespread use globally as well as in folklore medicine with other medications or stand-alone also could throw light on its safety in diverse clinical contexts.

Although there is a higher number of pre-clinical reports, and clinical studies carried out on diverse conditions and in diverse protocols, targeted safety and toxicity studies, both short-term and long-term as well as herb-drug interaction studies; a few recent studies have highlighted the potential hepatotoxic behavior of TC. Reports suggesting the beneficial role of TC in Auto-immune disease models such as EAE (Experimental Autoimmune Encephalo-myelitis) and RA (Rheumatoid Arthritis) related models, studies to evaluate the role of TC in pre-existing auto-immune disease models or other co-morbid conditions with and without concurrent drug use; may provide definite answers as regards speculated toxicity in patients with clinical AIH and HILI. Considering such wide spread use of the plant for various pathologies; it will not be prudent to discard the safety and efficacy aspects of *T. cordifolia* and label it as hepatotoxic.

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Rasyana Yoga

S.No	References	Yoga	Indication
1.	Ch chi 1/58	Dvitiya brahmarasayana	Rasayana chikitsa
2.	Ch chi 1/63	Chyavanprash	
3.	Ch chi 1/77	Haritakyadi yoga	
4.	Ch chi 1/30	Swarasa with roots and flowers - As medhya rasayana	

Chikitsa Yoga

S.No	References	Yoga	Indication
1.	Ch chi 3/198	Kashaya	Jwara chikitsa
2.	Ch chi 3/202	Kiratatiktadi Kashaya	Vishamajwara
3.	Ch chi 3/211	Shatyadi varga Kashaya	Sannipataja jwara
4.	Ch chi 3/222	Vasadi ghrita	Jeerna jwara
5.	Ch chi 3/247	Guduchyadi niruha basti	Jwara
6.	Ch chi 3/252	Patoladi anuvasana basti	Jwara
7.	Ch chi 3/267	Agurvadi taila	Sheeta jwara prashamana
8.	Ch chi 3/343	Kirata tiktakadi kwatha	Punaravartaka jwara
9.	Ch chi 6/29	Guduchi yoga (yavani, ushira, abhaya, guduchi)-Kwatha	Kaphaja prameha
10.	Ch chi 6/30	Guduchi yoga (Patola, Nimba, Amalaka, Amrita)-kwatha	Pittaja prameha
11.	Ch chi 7/124	Guduchi yoga (Guduchi, Apamarga, Devadaru)-Lepa	Vata kaphaja kushtha
12.	Ch chi 7/153	Mahakhadira ghrita	Sarvakushtha
13.	Ch chi 7/113	Kanaksheeri taila	Mandala kushta
14.	Ch chi 8/72	Shir pe parisheka swedana (with Kwatha)	Yakshma
15.	Ch chi12/25	Guduchi kalka with godugdha (Guduchi, Nagar, Danti)	Vatapittajanya shotha
16.	Ch chi 12/34	Punarnavadyarishta	Shotha
17.	Ch chi 15/190	Panchamakshara	Grahani
18.	Ch chi 16/63	pratahkalika yoga (Kwatha)	Kamala
19.	Ch chi 17/94	Nidigdhikadi yoga	Shwas-hikka
20.	Ch chi 18/35	Kantakari ghrita	Vataja kasa
21.	Ch chi 18/161	Guduchyadi ghrita	Kshayaja kasa

S.No	References	Yoga	Indication
22.	Ch chi 20/31	Guduchi hima pana (6 times water)	Pittaja Chhardi
23.	Ch chi 21/58	Drakshadi sheeta kwatha	Visarpa
24.	Ch chi 21/130	Guduchi kwatha	Granthi visarpa
25.	Ch chi 24/145	Guduchi swarasa with shunthi churna	Pittaja madatyaya (Alcoholic disease)
26.	Ch chi 25/75	Shoolanashaka sneha sharkara malaham	Shoola
27.	Ch chi 28/148	Balataila	Vatavyadhi chikitsa
28.	Ch chi 28/170	Vrushmuladi taila	Vatavyadhi
29.	Ch chi 29/71	Drakshadi ksheera	Vatashonita chikitsa
30.	Ch chi 29/103	Amrutadya taila	Vatarakta
31.	Ch chi 29/121	Guduchyadi taila	Vatarakta
32.	Ch chi 30/53	Kashmaryadi ghrita	Vataja yonivyapada
33.	Ch chi 30/58	Kwatha for yoni parishechana	Yonishool nashaka
34.	Ch chi 30/59	Guduchyadi taila for Yonipichu and Uttarbasti	Vataja Yonivyapad
35.	Ch chi 30/99	Guduchi kalka with madira –panartha	Kaphaja Asrigdara
36.	Ch chi 7/144	Mahatiktaka ghrita	Kushtha
37.	Ch chi 20/35	In ahara dravya	Kaphaja chhardi
38.	Ch chi 3/299	Guduchi Swarasa	Vishama Jwara
39.	Ch chi 6/31	Nimba, Arjuna, Amrita, Nisha, Utpala	Pittaja Prameha
40.	Ch chi 7/77	Kanaka Bindu Arishta	Vataja, pittaja, kaphaja Kushtha
41.	Ch chi 10/27	Vacha Shampakadi ghrita	Vataja, kaphaja apasmara
42.	Ch chi 16/134	Guduchi ghrita(swarasa, milk, buffallo ghree)	Haleemaka (Advanced liver diseases)
43.	Ch chi 17/102	Dashamooladi Yavagu	Kasa, Hikka, Swasa
44.	Ch chi 26/ 57	Saptacchhadadi Kwatha	Kaphaja Mutrakricchhra
45.	Ch chi 28/157	Amritadi Taila	Vata vyadhi
46.	Ch chi 30/279	Trayamana Guduchyadi Kwatha	Ksheera dosha
47.	Ch chi 22/45	Guduchi swarasa pana	Trushna
48.	Ch chi 23/70	Gandhahastinama agada	Visha chikitsa
49.	Ch chi 26/243	Amrutavhadi varga	Sannipataja netra roga
50.	Ch chi 26/283	Guduchi taila	Swarabheda chikitsa
51.	Ch chi 28/164	Amrutadya taila	Vatavyadhi
52.	Ch chi 28/172	Mulaka taila	Vatavyadhi
53.	Ch chi 29/73	Jeevakadi mahasneha	Vatarakta
54.	Ch chi 30/267	Kwatha for Dhatri (Lactating mother)	Stanyadosha nivarana
55.	Ch chi 30/261	Guduchi yoga (Amrita Saptaparna Kwatha)	Stanyashuddhi

Kalpa Sthana

S.No	References	Yoga	Indication
1.	Ch ka 1/22	Phalapippali……guduchi leha	For Vaman
2.	Ch ka 2/9	Gududchi kashaya	For Vamana in pitta shleshma jwara, Ardita
3.	Ch ka 7/19	Trivrita+ Guduchi churna	For Virechana in Vataja Pittaja Roga

Vimana sthana

1.	Ch vi 8/135	Vamana dravya kalpa sangraha	For vamana
2.	Ch vi 8/143	Tiktaskandha	For Asthapana Basti in Kapha pitta disorder (Per-rectal route)
3.	Ch vi 8/139	Madhura skandha	For Asthapana Basti in Vata pitta disorder (Per-rectal route)

Siddhi Sthana

1.	Ch si 3/13	Baladi niruhabasti	Vatavyadhi
2.	Ch si 3/39	Erandamooladi niruha basti	
3.	Ch si 4/4	Dashamooladi anuvasana taila	
4.	Ch si 9/8	Guduchi siddha taila – uttarabasti & Niruha basti	Marmaghat chikitsa
5.	Ch si 12/15	Mustadi yapana basti Erandamooladi yapana basti Baladi yapana basti dwitiya Brihatyadi Yapana Basti Sahacharadi yapana basti	Yapana basti
6.	Ch si 12/19	Chatusneha anuvasna basti	Kshatakshina, vandhya

Sutra Sthana

S.No	References	Yoga	Indication
1.	Ch su 2/12	Asthapana basti dravya	Basti dravya
2.	Ch su 2/14	Anuvasna basti dravya	_____
3.	Ch su 3/3	Bahya prayogartha churna	_____
4.	Ch su 3/22	Ghrita with Rasna and Guduchi	Pradeha for Vatarakta

S.No	References	Yoga	Indication
5.	Ch su 4/ 21	Snehopaga mahakshaya	Mahakashaya
6.	Ch su 4/ 5	Sandhaniya mahakshaya	
7.	Ch su 4/50	Vayasthapana mahakshaya	
8.	Ch su 4/11	Truptighna mahakshaya	
9.	Ch su 4/12	Stanyashodhana mahakshaya	
10.	Ch su 4/29	Trushna nigrahana mahakashaya	
11.	Ch su 4/41	Dahaprashamana gana	
12.	Ch su 21/22		Medoroga chikitsa
13.	Ch su 26/49	Viruddha veerya dravya	_____
14.	Ch su 27/106	Guduchi shaka	Annapana vidhi adhyaya
15.	Ch su 14/31	Nadi sweda dravya (Kwatha)	_____
16.	Ch su 25/40	Agrya sangraha	Best in class for Sangrahaka, vatahara, dipana, shonita-shleshmavi-bandhaprashamana
17.	Ch su 27/4	In hitakara ahara	Annapana vidhi adhyaya

References from classical books | Sushruta Samhita

Uttara Tantra

S.No	References	Yoga	Indication
1.	Su u 19/13	Guduchi siddha ghrita	Aschotana
2.	Su u 28/7	Aushadhi dharana	For Sishu rakshana
3.	Su u 39/152	As a shaka dravya	Jwara
4.	Su u 39/170	Guduchi Kashaya	Vataja jwara – In Kaphanubandha – guduchi shruta kashaya In Vatanubandha –Guduchi Sheeta kashaya
5.	Su u 39/173	Drakshadi kashaya	Vataja jwara
6.	Su u 39/174	Guduchi swarasa with guda	Vataja jwara
7.	Su u 39/178	Guduchyadi kwath	Pittaja jwara
8.	Su u 39/186	Guduchi kwatha	Kaphaja jwara
9.	Su u 39/213	Kwatha	Vishamajwara
10.	Su u 39/221	Guduchyadi ghrita	Kshaya –shwasa –kasa-jeerna jwara
11.	Su u 39/226	Patolyadi ghrita	Apachi-kushta-jwara

S.No	References	Yoga	Indication
12.	Su u 39/243	Guduchi swarsa siddha ghrita	Jeernajwara-shopha-panduroga
13.	Su u 39/245	Triphaladi ghrita	Parisarpa, jwara, shwasa, gulma
14.	Su u 40/50	Guduchi with ushnajala	Aama pachanartha
15.	Su u 44/36	Guduchi siddha ghrita	Lagharaka roga chikitsa
16.	Su u 49/24	Guduchi sheetkashaya pana	Sannipatika chhardi chikitsa
17.	Su u 39/199	Kashaya	Vata pitta jwara kashaya
18.	Su u 39/257	Ksheerivrukshadi taila	Jeerna jwara
19.	Su u 41/38	As aahara	Shosha chikitsa
20.	Su u 52/42	Agastyavaleha	Rajayaksma, kasa
21.	Su u 57/11	Leha	Vatadi arochakara

Chikitsa Sthana

S.No	References	Yoga	Indication
22.	Su chi 1/115	Patradana	Kaphaja vrana
23.	Su chi 2/74	Manjishtadi taila	vranaropana
24.	Su chi 2/39	Chandandi taila	Vrana ropana
25.	Su chi 5/8	Guduchi kwatha	Pitta pradhana vatarakta
26.	Su chi5/13	Patoladi kashaya	Vatarakta
27.	Su chi 6/13	Aushadhi chikitsa	Arsha (internal piles)
28.	Su chi 9/7	Guduchi siddha sneha	Vataja kushta
29.	Su chi 9/8	Mahatiktaka ghrita	Kushtha
30.	Su chi 10/4	Mantha	Mahakushta chikitsa
31.	Su chi10/13	Guduchi swarsa/ kwatha/ ghrita	Sarvakushtha nashana
32.	Su chi 11/9	Kashaya pana	Sarpimeha
33.	Su chi 15/44	Guduchi siddha taila	Mudagarbha chikitsa
34.	Su chi 20/50	Upanahaan	Valmika chikitsa
35.	Su chi 27/7	Vidanga + yashtimadhu churna with guduchi kwatha	Rasyana yoga
36.	Su chi 37/20	Bhutikadi taila	Vata vikara
37.	Su chi 37/34	Triphaladi taila	Sthulata, kaphaja roga
38.	Su chi 38/43	Asthapana basti	Vatahara
39.	Su chi 38/47	Guduchi-triphaladi basti	Asthapana basti
40.	Su chi 18/5	Guduchi lepa	Vataja granthi chikitsa
41.	Su chi 18/45	pralepa	Vataja galaganda

42.	Su chi 18/47	Amritadi taila panartha	Galaganda
43.	Su chi 19/57	Guduchi lepa with gomutra	Kaphaja shlipada
44.	Su chi 38/70	Rasnadi asthapana basti	Vatavyadhi
45.	Su chi 38/105	Mustadi basti	Vatrakta, meha

Sutra Sthana

S.No	References	Yoga	Indication
46.	Su su 12/23	Guduchi lepa	Samyaka dagdha chikitsa
47.	Su su 25/21	Guduchi tana	For seevana karma
48.	Su su 37/23	Varti	Vrana ropana
49.	Su su 42/11	Tikta varga aushadhi	Class of Tikta plants
50.	Su su 44/6	Virechana yoga	Kaphaja vikara
51.	Su su 46/262	Tiktapraya dravya	Raktapittahara, Kushtha, Meha, Jwarahara
52.	Su su 46/270	Guduchi guna	Kapha-pittahara, Tikta rasa
53.	Su su 46/254	As a shaka	Ushna, swadu, tikta, vata prashamana

Guduchi in Gana

54.	Su su 38/6	Aragvadhadhi gana	Vrana shodhana
55.	Su su 38/29	Shyamadi gana	Gulma, visha
56.	Su su 38/33	Patoladi gana	Pitta kapha arochanashaka
57.	Su su 38/50	Guduchyadi gana	Sarva jwara
58.	Su su 38/72	Panchavalli gana	Raktapittahara, Sarvameha hara

Kalpa Sthana

59.	Su ka 1/54	Guduchi for pana and anulepna	For *vishakta abhyanga chikitsa*
60.	Su ka 2/45	Yavagu made from guduchi kwatha	For *the chikitsa between the vegas of visha*
61.	Su ka 7/29	Guduchi kwath	Mushaka dansha chikitsa
62.	Su ka 7/33	Guduchi kalka lepa	Mushaka dansha chikitsa

Rasayana Yoga

S.No	References	Yoga	Indication
1.	AH U 1/44	Ashtanga ghrita	Vak-medha-smriti-buddhikrut
2.	AH U 1/46	Vachadi ghrita	Medha-smriti-vanhikruta
3.	AH U 39/44	Guduchi rasa	Medhya rasayana
4.	AH U 39/104	Shunthi adi rasayana	Rasayana
5.	AH U 39/34	Chyavanaprash	Rasayana
6.	AH U 39/60	Guduchi sevana	Medha, dhi, vaya, sthairya, bala prada
7.	AH U 39/159	Shwadanshtradi churna	Rasayana, vrushya, balya
8.	AH Chi 3/133	Vashishta haritaki rasayana	Rasayana

Uttara Shtana - Chikitsa Yoga

9.	AH U 2/13	Guduchi kwatha	Pittadushita stanyachikitsa
10.	AH U 2/25	Guduchi yoga	Stanyadoshahara
11.	AH U 9/27	Guduhci kwatha	Kukunaka chikitsa
12.	AH U 13/12	Maha triphala ghrita	Drushtivikarjit
13.	AH U 13/68	Guduchi siddha ghrita	Kaphaja timira chikitsa
14.	AH U 22/6	*Guduchi siddha ghrita (Abhyanga)*	Oshtharoga
15.	AH U 22/68	Guduchi siddha taila	Vataja galaganda
16.	AH U 22/78	Guduchi kalka / kwatha -Gandush	Mukharbuda
17.	AH U 22/97	Kshudradi kawala	Mukharoga
18.	AH U 22/104	Patoladi kwath	Mukharoga
19.	AH U 28/38	Guggulu yoga	Prameha pitika, bhagandara
20.	AH U 32/9	Guduchi patra lepa	Valmika chikitsa
21.	AH U 34/28	Kashmaryadi ghrita	Vataja yonivikruti
22.	AH U 34/33	Guduchi kwath sechana	Vataja yonivyapada
23.	AH U 35/21	Guduchi siddha yavagu	Visha nashaka
24.	AH U 35/57	Guduchi patra sevana	In agnimandya due to Garavisha
25.	AH U 38/20	Guduchi lepa	Mushaka dansha
26.	AH U 38/26	Guduchi siddha ghrita	Mushaka visha chikitsa
27.	AH U 40/50	Agrya sangraha	Guduchi – vatasraroge

Chikitsa Sthana

S.No	References	Yoga	Indication
28.	AH Chi 1/46	Guduchi kwatha & sheeta kashaya	Jwara shamana aushadha yoga
29.	AH Chi 1/50	Kashaya	Vishama jwara
30.	AH Chi 1/52	Kashaya	Vataja jwara
31.	AH Chi 1/60	Kashaya	Vata-kaphaja jwara
32.	AH Chi 1/61	Kashaya	vata-kaphaja jawra
33.	AH Chi 1/64	Kashaya	Pitta-kaphaja jawra
34.	AH Chi 1/66	Kashaya	*Vata kaphaja jwara* with *kasa, shwasa, parshwashoola*
35.	AH Chi 1/94	Guduchi siddha ghruta	Jeerna jwara
36.	AH Chi 1/139	Guduchi tailapaka - abhyanga	In jwara - sheetashamaka upaya
37.	AH Chi 1/154	*Guduchi* with *guda*	Rasayana vidhi prayoga in jwara
38.	AH Chi 3/3	Guduchi siddha ghrita	Vataja-kasa nashaka
39.	AH Chi 3/58	Punarnavadi ghrita	Kasa, Vishama Jwara
40.	AH Chi 3/63	Vyaghri leha	Kasa, Shwasa
41.	AH Chi 3/164	Guduchi siddha ghrita/ Vrishadi ghrita	Kasa, jwara, aruchi
42.	AH Chi 4/22	Guduchi yusha	Shwasa, hikka
43.	AH Chi 4/24	Guduchi Kashaya –peya	Shwasa, hikka
44.	AH Chi 5/61	Amrutakshara jala	Praseka chikitsa (In rajayakshma)
45.	AH Chi 6/14	Guduchi rasa pana	Pittaja chhardi chikitsa
46.	AH Chi 7/25	Guduchi rasa pana	Madatyaya with kasa, sarakta nishthiva, trushna
47.	AH Chi 8/49	Guduchi lepa inside the pot of takra	Arsha
48.	AH Chi 11/12	Guduchi siddha kwatha with madhu/ peya	Kaphaja mutraghata
49.	AH Chi 12/6	Guduchi swarasa with madhu	Prameha nashana yoga
50.	AH Chi 12/8	Guduchi kwatha	Pittaja prameha
51.	AH Chi 13/4	Guduchi lepa	Pittaja vidradhi chikitsa
52.	AH Chi 14/14	Dadhika ghrita	Gulma, apasmara
53.	AH Chi 16/13	Vasadi kwatha with madhu	Panduroga
54.	AH Chi 16/53	Guduchi rasa siddha ghrita	Halimaka chikitsa
55.	AH Chi 17/40	Amrutadi churna with gomutra pana	Shotha, udara
56.	AH Chi 18/6	Guduchi sheetakashaya	Trushna, visarpa
57.	AH Chi 18/30	Guduchi sevana	Granthi bhedana upachara
58.	AH Chi 19/2	Guduchi siddha sneha	Vata pradhana kushtha
59.	AH Chi 19/9	Mahatiktaka ghrita	Kushtha
60.	AH Chi 19/18	Vajraka ghrita	Visarpa, jwara, kushtha
61.	AH Chi 19/39	Guduchi siddha ghrita	Kushtha
62.	AH Chi 13/86	Guduchi lepa	Kushtha

S.No	References	Yoga	Indication
63.	AH Chi 21/58	Nimbadi ghrita /Panchatikta Gugglu ghrita	Vatvyadhi chikitsa
64.	AH Chi 21/73	Balataila	Shreshta vatavyadhi nashana
65.	AH Chi 22/7	Guduchi siddha ghrita	Vatarakta
66.	AH Chi 22/10	Guduchi kwatha/ ghrita	Vatarakta (Pittaja)
67.	AH Chi 22/15	Guduchi kwatha with madhu	Kapha pradhana vataarkta

Sutra Sthana

68.	AH Su 6/75	Guduchi shaka	Grahi, kapha pittajit
69.	AH Su 7/20	Guduchi kalka lepa /kwatha	Sparshaja visha chikitsa
70.	AH Su 10/29	Tikta-skandha dravya	
71.	AH Su 14/22	Guduchi swarasa with madhu	Sthulata chikitsa
72.	AH Su 30/51	Guduchi churna with ghruta – lepa	Samyaka dagdha chikitsa

Gana

73.	AH Su 15/12	Padmakadi gana	Stanyakara, prinana, jeevana
74.	AH Su 15/15	Patoladi gana	Kamala, Kapha, pitta, Jwara hara
75.	AH Su 15/16	Guduchyadi gana	Pitta-shleshma jwara, chhardi
76.	AH Su 15/17	Aragvadhadi gana	Dushta-vrana vishodhana
77.	AH Su 15/45	Shyamadi gana	Hrutruja, mutrakruchha

Kalpa Sthana

S.No	References	Yoga	Indication
78.	AH K 4/1	Baladi kalpa for basti	Bruhana
79.	AH K 4/7	Erandamooladi kalpa	Niruha basti prayoga
80.	AH K 4/37	Yapana rajabasti	Mamsagnibalashukra vardhana
81.	AH K 4/55	Dashmooladi sneha –anuvasana	Vataja roga
82.	AH K 5/19	Guduchi patra with gomutra –basti	Urdhwa-maruta vyapada

Sharira Sthana

S.No	References	Yoga	Indication
83.	AH Sha 2/7	Guduchi kwatha	For Garbhini in rakta darshana & amatisara

Chakradatta - Rasayana Yoga

S.No	References	Yoga	Indication
1.	10/48	Chyavanaprasha	Rasayana
2.	66/13	Guduchi rasa (whole plant)	Chatvari medhya rasyanani
3.	66/23	Guduchyadi rasayana	Tribhidine shloka sahsra dharinam
4.	66/173	Shiva gudika	Vajikaran
5.	67/15	Narsinha churna	Vrushya

Chikitsa yoga

S.No	References	Yoga	Indication
6.	1/41	Guduchi shaka	Pathya ahara in jwara
7.	1/69	Guduchi kwatha	Vataja jwara
8.	1/70	Kiratatiktadi kwatha	Vataja jwara
9.	1/75	Bilwadai kwatha	Vataja jwara
10.	1/77	Guduchyadi kwatha	Vataja jwara
11.	1/78	Drakshadi kwatha	Vataja jwara
12.	1/79	Shatavaryadi kwatha	Vataja jwara
13.	1/82	Lodhradi kwatha	Pittaja jwara
14.	1/89	Parpatadi Kashaya	Pitttaja jwara
15.	1/104	Nimbadi kwatha	Kaphaja jwara
16.	1/107	Triphaladi kwatha	Kaphaja jwara
17.	1/114	Navanga kashaya	Vata-pitta jwara
18.	1/116	Kiratatiktadi Kashaya	Vata-pitta jwara
19.	1/117	Nidigdhikadi kashaya	Vata-pitta jwara
20.	1/118	Panchbhadra Kashaya	Vata-pitta jwara
21.	1/122	Patoladi kashaya	Pitta-kaphaja jwara
22.	1/123	Guduchyadi kwatha	Sarvajwara
23.	1/124	Chaturbhadraka -pathasaptako	kaphaja-Pittaja jwara
24.	1/125	Kantakaryadi kwatha	Pitta-kaphaja jwara

S.No	References	Yoga	Indication
25.	1/129	Amrutashtaka kwatha	Pitta-kaphaja jwara
26.	1/132	Panchtikta kwatha	Ashtavidha jwara
27.	1/142	Kshudradi kwatha	Tridoshaja jwara
28.	1/144	Musatdi kwatha	Vata kapha jwara
29.	1/178	Shatyadi kwatha	Sannipataja jwara
30.	1/185	Karvyadi kwath	Abhinyasa jwara
31.	1/190	Vyoshadi kwatha	Tridoshaja jwara
32.	1/201	Nidigdhikadi kwatha	Jeerna jwara
33.	1/203	Guduchi-panchamoolakwatha	Jeerna jwara
34.	1/206	Kwatha	Vishamajwara
35.	1/207	Santatadihara pancha kwatha	Vishamajwara
36.	1/210	Guduchyadi kwatha	Jwara
37.	1/211	Mustadi kwatha	Vishamajwara
38.	1/212	Mahaushadhi kwatha	Tritiyaka jwara
39.	1/258	Vasadi ghrita	Jeerna jwara
40.	1/260	Guduchyadini pancha ghritani	Jwara
41.	2/3	Pathadi kashaya	Jwara, amatisara
42.	2/4	Nagaradi kashaya	Sarva atisara nashana, sarva jwarahara
43.	2/6	Guduchyadi kwatha	Jwara atisara
44.	2/10	Panchamulyadi kwatha	Atisara
45.	2/15	Nagaradi kwatha	Jwaratisara
46.	2/28	Kiratatiktadi kwath Prathama	Shotha, atisara, jwara
47.	2/29	Kiratatiktadi kwatha –apara	Shotha, atisara, jwara
48.	4/7	Shunthyadi kwatha	Grahani
49.	5/105	Sinhyamruta ghrita	Arsha, meha
50.	5/157	Guduchi lepa	Samyakadagdha
51.	5/169	Bhallataka lauha	Arsha , grahani
52.	6/9	Vishwadi kwatha	Agnimandya
53.	6/14	Vidangadi leha	Agnimandya
54.	6/87	Karanjadi kwatha	Visuchika
55.	8/8	Phalatrikadi kwatha	Pandu, kamala
56.	8/25	Swarasa prayoga	Kamala
57.	9/82	Khandakadyau lauha	Raktapitta
58.	10/10	Ashwagandhadi Kashaya	Yakshma
59.	10/26	Shrungyarjunadi churna	Yaksha

S.No	References	Yoga	Indication
60.	10/65	Parashara ghrita	Rajayakshma
61.	11/50	Kantakari ghrita	Vataja Kasa, Agni deepana
62.	12/11	Parnas panchakam	Kasa, shwasa
63.	12/15	Shrungyadi churna	Shwasa
64.	15/10	Guduchyadi kwatha	Pitta-amla sambhavam Chhardi
65.	15/16	Guduchi hima	Chhardi
66.	15/19	Bilwa guduchi Kashaya with madhu	Traya-chhardi
67.	15/28	Padmakadya ghrita	Trushna, chhardi
68.	16/1	Guduchi swarasa	Trushna
69.	17/6	Mahaushadhadi kwatha	Murchha, mada
70.	22/42	Dashamoolyadi kwatha	Grudhrasi
71.	22/65	Guduchi kwatha	Koshtrushirsha
72.	22/72	Trayodashanga guggulu	Vatavyadhi
73.	22/163	Dashanga masha taila	Vatavyadhi
74.	22/168	Maha masha taila	Vatavyadhi
75.	22/228	Ekadashashatikam prasarini taila	Vatavyadhi
76.	23/4	Trikarshika kwatha	Vatarakta with Ama, Kushtha
77.	23/5	Vatsadini kwatha	Vatarakta
78.	23/7	Munditika with guduchi kwatha	Vatarakta
79.	23/8	Haritaki with guduchi	Vatarakta
80.	23/9	Guduchya shata prayoga with eranda taila	Vatarakta
81.	23/12	Patoladi kwatha	Sadaha vatarakta
82.	23/15	Katukadi	Kaphaja vatarakta
83.	23/17	Kokilakshadi kwatha	Vatarakta
84.	23/20	Pathyadi prayoga trayam – Guduchi kwatha with haritaki	Vatarakta
85.	23/21	Guduchi taila	Vatarakta , Kushtha
86.	23/23	Navakarshika Kashaya	Vatarakta
87.	23/26	Guduchi ghrita	Vatarakta, Kushtha
88.	23/28	Amrutadya ghrita	Uttana & Gambhira Vatarakta
89.	23/37	Guduchyadini tailam	Vatarakta
90.	23/48	Kaishor guggulu	Vatarakta
91.	23/54	Amruta guggulu	Vatarakta , Kushtha, Arsha, Mandagni
92.	23/61	Punarnava guggulu	Vatarakta , Kushtha

S.No	References	Yoga	Indication
93.	23/63	Yogasaramruta	Vatarakta , Kshaya, Kushtha, Karshya
94.	23/73	Bruhat guduchi taila	Vatarakta (through oral, topical and perrectal route)
95.	24/4	Bhallatakadi Kwatha	Urusthambha
96.	24/14	Amruta guggulu	Urusthambha
97.	25/3	Shatyadi kwath	Amavata (for Pachana)
98.	25/5	Rasna dashamoolaka	Amavata
99.	25/7	Rasnapanchaka	Sama vata, sandhi-asthi majjagata vata
100.	25/8	Rasnasaptakam	Jangha-uru-prushtha-trika -parshwashoola
101.	25/10	Haritaki with guduchi	Amavata
102.	25/19	Alambushadi churna	Amavata (for inflammation and swelling of joints)
103.	25/21	Bhagottara alambushadi churna	Amavata (for inflammation and swelling of joints)
104.	25/41	Bruhatsinhanad guggulu	Amavata
105.	25/60	Amrutadya ghritam	Vatarakta, amavata
106.	27/58	Dhatrilauha	Parinama shola
107.	32/2	Amrutadi kwath	Sashoola mutrakruchha
108.	32/31	Sukumarakam ghrita	Mutrakruchha
109.	34/41	Varun ghrita	Ashmari
110.	35/9	Kharjuradi kwatha	Raktameha
111.	35/13	Pathadi churna	Kushtha, sarpimeha
112.	35/63	Kushavaleha	20 prameha, mutraghata, ashmari
113.	36/17	Amruta guggulu	Sthoulya, bhagandara
114.	36/31	Triphaladya taila	Sthoulya
115.	37/49	Dashamooladi kwatha	Jalodara, Shotha, shleepada
116.	37/50	Haritakyadi kwatha	Shotha, udara
117.	37/52	Punarnavashtaka kwatha	Sarvangashotha, udara
118.	37/53	Punarnavadi kwatha with gomutra	Twakdosha, udara
119.	37/55	Punarnavadi churna	Sarvagatra shotha
120.	38/15	Manadya gudika	Yakrutaplihodara , Gulma
121.	39/3	Trivrutadi kwatha	Pittaja shotha
122.	39/8	Punarnavadi kalka & kwatha	Kaphaja shotha
123.	39/11	Punarnavashtaka kwatha	Sarvanga shothodara

S.No	References	Yoga	Indication
124.	39/21	Sinhasyadi kwatha	Shotha
125.	39/25	Punarnavadi	Shotha
126.	39/44	Punarnavavaleha	Shotha, shoola
127.	40/11	Rasnadi kwatha	Antravriddhi
128.	40/31	Shatapushpadyam ghrita	Vriddhi, antravriddhi
129.	41/15	Amrutadya taila	Galganda
130.	41/39	Hinsradi lepa	Vatika granthi
131.	42/16	Guduchi swarasa prayoga	Shlipada
132.	42/17	Samavruddhadaraka churna	Shlipada, sthaulya, Amavata
133.	44/73	Amrutadya guggulu	Galganda
134.	44/75	Amrutadi vatika guggulu	Vranashotha, Vatarakta
135.	46/2	Vatapatradi lepa	bhagandara
136.	46/13	Saptavinshitika guggulu	Bhagandara
137.	47/3	Patoladi kwatha	Updansha
138.	50/8	Aragvadhadya shata churna pradeha	Kushtha, Kilasa (vitiligo)
139.	50/60	Chhinnaswarasa	Kushtha
140.	50/77	Panchanimbam	Kushtha , Vicharchika
141.	50/99	Panchatikta ghrita	Kushtha
142.	50/108	Mahatiktaka ghrita	Kushtha, Raktapitta
143.	50/114	Mahakhadirakam ghrita	Kushtha
144.	50/118	Panchatiktaghrita guggulu	Visha, Vataja kushtha
145.	50/122	Vajrakam ghrita	Vajravata kushthahara
146.	50/129	Mahatrunaka taila	Sarva Twakadoshaharana
147.	50/140	Bruhanmarichyadi taila	Twakadosha
148.	51/3	Visarpokta amrutadi	Udardahara yoga
149.	52/8	Patola-vishwadi kwatha	Shoola, bhrama, arochaka
150.	52/9	Yavaadi kwatha	Amlapitta , Aruchi
151.	52/14	Chhinnadi kwatha	Amlapitta
152.	52/17	Chhinodbhavadi shadanga kwatha	Amlapitta
153.	52/19	Sinhasyadi kwatha	Amlapitta
154.	52/54	Drakshadyam ghrita	Amlapitta, grahani
155.	53/20	Navakashaya guggulu	Visarpa , Visha
156.	53/21	Amrutadi kwatha	Visarpa, sphota
157.	53/22	Patolamrutadi kwatha	Visphota, jwara
158.	53/23	Patola-triphaladi kwatha	Visarpa , Kandu, Twak dosha
159.	53/35	Vrushadyam ghrita	Visarpa , Kushtha, Gulma
160.	53/28	Kundalyadi kwatha	Visphota
161.	54/14	Dwipanchamooladi kwatha	Vataja masurika
162.	54/15	Guduchyadi kwatha	Vataja masurika
163.	54/21	Patoladi kwatha	Visphota, jwara

S.No	References	Yoga	Indication
164.	54/25	Khadirashtakam	Romantika, masurika , Kushtha
165.	54/26	Amrutadi kwatha prayoga	Pitta-kaphaja masurika
166.	54/30	Guduchyadi kwatha	Vatashamana
167.	55/110	Adityapaka guduchi taila	Kesharopana
168.	55/111	Chandanadya taila	Keshya
169.	56/93	Jatipatradi gandusha	Mukhapaka
170.	58/31	Chitraka haritaki	Nasa roga chikitsa, kshaya, kasa, peenasa
171.	59/48	Bruahad vasadi kwatha	Netraroga
172.	59/175	Mahatriphaladyam ghrita	Netraroga
173.	60/56	Pasting with guduchi , Shirobasti	Shirakampa chikitsa
174.	61/2	Guduchi swarasa with sharkara + madhu	Pittaja pradara
175.	62/4	Vachadi churna	Yonivyapada chikitsa
176.	62/45	Trayodashanga phalaghrita	Yonishoola , yonidoshahara
177.	63/39	Amrutadi kwatha	Sutika jwara
178.	63/55	Amrutadi kwatha	Pittadushti in Dhatri and Kumara

Ashtanga Sangraha Uttara Tantra

S.No.	Refer-ences	Disease	Dosage form	Remark
1.	1/68	Balaroga	Ghrita	———
2.	2/13	Pitta Dusti Stnaya	Ghrita	Abhyanga, Pradeham, Pariseka
3.	2/18	Stanyadusti	Kwatha	alongwith Bhunimba, Amrita, Kutajaphala, sariva
4.	2/30	Stanyadosha Chikitsa	Kwatha	Sandra stanyadoshahara
5.	6/7	Balopacharaniyam	Bandhana In Neck & Head	Somvalli
6.	12/14	Kukunaka Chikitsa	Decoction	for lactating mother

S.No.	References	Disease	Dosage form	Remark
7.	12/15	Kukunaka Chikitsa	Pariseka	Eye Wash (with other drugs)
8.	16/13	Netraroga	Ghrita	Mahatriphala Ghrita
9.	16/56	Kaphaj Timira	Kwatha	As snehana before Virechana
10.	26/5	Pittaj and Abhighataj ostha roga	Ghrita	For Abhyanga
11.	26/39	Talupaka	Decoction	Gargling
12.	26/47	Gala Vidradhi	Taila	Nasal Medication
13.	26/48	Slesma Galaganda	Fomentation & Paste	For external and intrnal use
14.	26/60	Arbuda Chikitsa	Decoction	For Gandusha dharana
15.	30/20	Shoola, Daha	Utkarika	Local fomentation
16.	30/58	Ropana in Vrana	Saptakarma	Multiple formulations for wound healing
17.	30/79	Varnyakrit	Churna	With other , for complexion promoting
18.	31/30	Mushka abhighata	Taila	For wound healing
19.	33/48	Bhagandara, sthaulya	Paana	With honey
20.	35/6	Vaatjanya Granthi	Lepa	To be applied warm with milk
21.	35/23	Varnavibhag	Lepa	———
22.	37/13	Valmika Chikitsa	Lepa	After shodhana & Raktamokshana
23.	39/34	Vaat Yonivyapat	Ghrita Paana	For infertility too
24.	39/34	Vaat Yonivyapat	Kwatha (Pariseka)	For vaginal wash
25.	39/73	Kapha Prdhan Asrugdhar	Paana	———
26.	40/55	Vishaghani Peya	Kwatha Yavagu	———
27.	40/88	Aushanas Agada	Agada	———
28.	40/94	Vishapratisedha	Anjana, Lepa	———
29.	40/120	Vishapratisedha	Churna	In food poisoning
30.	44/46	Vaatika Visha	Lepa	———
31.	46/19	Moosika Visha	Lepa	———
32.	46/21	Mooska Visa	Lepa	———
33.	46/39	Moosika Visha	Ghrita	———
34.	46/31	Moosika Visha	Kwatha	———
35.	46/58	Mooska Visa	Kalka Ghrita Siddha	———
36.	49/33	Rasayana (Amalaka Rasayana)	Churna	———

S.No.	Refer-ences	Disease	Dosage form	Remark
37.	49/40	Rasayan (in chyavana prasha avaleha)	Kwatha	Amritadvyam
38.	49/63	Rasayan Medhavardhaka	Swarasa	———
39.	49/122	Rasayan Vidanga Pryoga	Kwatha	———
40.	49/135	Rasayan Bakuchi	Kwatha	———
41.	49/148	Apatantaka	Kwatha	———
42.	49/271	Pittakaphajanya Roga	Kwatha	———
43.	49/286	Pitta Roga	Kwatha	
44.	49/309	Rasayana	Kwatha	Shiva Gutika
45.	49/361	Rasayana	Swarasa	———
46.	049/381	Rasayana	Churna	Guduchi+ gokshura+ amalaki with honey and ghee for longeivity

ARTICLES SCREENED IN PUBMED

PubMed indexed articles published till 5th March 2022 were reviewed using the search strategy "("Giloy" [All Fields] OR (("tinospora"[MeSH Terms] OR "tinospora" [All Fields]) AND "cordifolia" [All Fields]) OR "Guduchi" [All Fields]) AND ("hepatitis" [All Fields] OR "adverse drug"[All Fields] OR ("toxic" [All Fields] OR "toxical"[All Fields] OR "toxically" [All Fields] OR "toxicant" [All Fields] OR "toxicant s" [All Fields] OR "toxicants" [All Fields] OR "toxicated" [All Fields] OR "toxication" [All Fields] OR "toxicities" [All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity" [All Fields] OR "toxicity s" [All Fields] OR "toxics"[All Fields]) OR "cirrhosis" [All Fields] OR "autoimmune" [All Fields] OR "hepatic failure"[All Fields] OR "liver dysfunction"[All Fields])" with the use of article differentiation using filters.

Ninety publications (including animal studies *plus* 1 retracted article) that mentioned interaction between liver and *Tinospora cordifolia* were retrieved of which 27 (including 1 retracted article) were in context with humans. With clinical trials as filter, 14 publications were retrieved of which 10 belonged to the rubric of randomized controlled trials.

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VARIOUS TINOSPORA SPECIES

1. T. arfakinsa
2. T. baenzigeri
3. T. barkis
4. T. celebica
5. T. cordifolia
6. T. crispa
7. T. dentata
8. T. dissitiflora
9. T. esiangkara
10. T. formani
11. T. fragosa
12. T. glabra
13. T. glandulosa
14. T. guangxiensis
15. T. hainanensis
16. T. hirsute
17. T. homosepala
18. T. macrocarpa
19. T. maqsoodiana
20. T. merriliana
21. T. neocaledonica
22. T. nudiflora
23. T. orophila
24. T. palminervis
25. T. sagittata
26. T. siamensis
27. T. sinensis
28. T. smilacina
29. T. subcordata
30. T. sumatrana
31. T. teijsmannii
32. T. tenara
33. T. tinisporoides
34. 34. T. trilobat

SUMMARY OF CLINICAL TRIALS DONE ON GUDUCHI

Author / year	Place of study	Study design	Inclusion criteria	Exclusion criteria	Random-ization	Allocation conceal-ment	
Dev pura G 2021	Jaipur India	Randomized Placebo controlled double blind trial	Asymptomatic/ mild COVID 19 RT PCR positive 15-80 years of age	Severe symptomatic disease Co-morbidities	Done through computer generated random number	Informa-tion not available	
Nair S 2020	Maha-rashtra, India	Non ran-domized Before and after study No placebo group	participants having gingival inflammation (Loe and Sillness index, [16] score 1.12) and a minimum of 28 natural teeth in the mouth.	presence of any systemic diseases, history of antibiotic therapy or mouthwash used in the previous 1 month, malocclusion, periodontitis, history of smoking and the presence of grossly carious teeth.	None	None	
Kumari S 2016	Maha-rashtra India	Non-ran-domized	twelve alcoholic and fourteen non-alcoholic male volunteers	body mass index >30 kg/ m2, blood pressure >160/90 mm Hg, total cholesterol >7.5 mmol/L, present or prior history of cardiovascular disease, diabetes mellitus, respiratory, gastrointestinal, hepatic, renal, endocrine, or reproductive disorders; or use of lipid-lowering agents, anti-hypertensive agents.	None	None	

	Blinding	Blinding of outcome assess-ment	Treatment arm	Placebo arm	Primary outcome measure	Other outcome measures	Adverse events
	Patient and caregiver were blinded	Not men-tioned	Giloy Ghanvati (*Tinospora cordifolia*) 1 g and 2 g of Swasari Ras (traditional herbo-mineral formulation) and 0.5 g each of Ashwagandha (*Withania somnifera*) and Tulsi Ghanvati (*Ocimum sanctum*) twice per day for 7 days.	Similar looking tablets	Negative RT PCR	IL 6 Hs CRP TNF alpha	Details NOT available. But the authors state that no rise in AST ALT bilirubin Urea and creatinine at day 7
	None	None	50 gms of coarse *T. cordifolia* powder along with freshly picked mint leaves (45 leaves) from the ayurveda nursery were boiled in 1800 ml of water till 1/16th proportion (200 ml) was obtained. Mouth wash twice daily for 21 days	None	Plaque index Gingival index Gram postive, gram negative and s.mutans count	none	None
	None	None	100 ml TCJ (3.0 gm solid extract) early in the morning with an empty stomach for 14 days	None	Cholestrol and steroid levels	None	None mentioned

Author / year	Place of study	Study design	Inclusion criteria	Exclusion criteria	Random-ization	Allocation conceal-ment	
Kurian GA 2014	Kerala India	Randomized case control study	Patients were eligible to participate if they had type 2 diabetes mellitus according to World Health Organization (WHO) criteria were between 35-60 years.	Patients were excluded if they had an HbA1c>9.2%: significant renal, hepatic or cardiac disease; cancer; drug or alcohol abuse; severe hypocalcemia, anemia, hemoglobinopathy; pregnant and nursing patients.	Details not available	Details not available	
Chopra A 2013	Pune India	Randomized controlled trials	Patients of either sex in the age range 4070 years with a diagnosis of knee OA as per modified ACR classification [16] criteria (the lower age limit was 40 years) and pain visual analogue scale (VAS) score 54 cm in one or both knees while performing a weight-bearing activity (e.g. walking, standing, climbing staircase) during the preceding 24 hours were included in the study; ambulant patients required frequent analgesics.	Pregnant or lactating women or women with childbearing potential and not following adequate contraception; patients with non-degenerative joint disorders, severe disabling arthritis (including wheelchair bound) or a history of spine and lower limb surgery; patients on medication likely to influence efficacy evaluation (except paracetamol rescue); patients with a history of peptic ulcer bleed or recent active peptic ulcer and patients with any unstable severe medical diseases were excluded.	Yes Computer generated random numbers and block random-ization	Not mentioned	

	Blinding	Blinding of outcome assess-ment	Treatment arm	Placebo arm	Primary outcome measure	Other outcome measures	Adverse events
	Details not available	Details not available	Poly herb named G-400 contains a mixture of the following herbs expressed as percentage in dry weight: 30% Salacia Oblonga leaves, 10% Tinospora Cordifolia, 10% Emblica officinalis, 10% Curcuma longa and 40% Gymnema sylvestre. Plus usual treatment for DM		Fasting and postpran-dial blood glucose levels measured after 8 wk of G-400 treatment		None
	Yes	Not mentioned	Ayurvedic formulations (extracts of Tinospora cordifolia, Zingiber officinale, Emblica officinalis, Boswellia serrata)	Oral glucos-amine sulphate (2g daily) and celecoxib (200 mg daily) were administered in a similar manner (three times a day in equally divided doses).	Primary efficacy variables were active body weight-bearing pain (visual analogue scale) and modified WOMAC pain and functional difficulty Likert score		Seven patients in the Ayurvedic intervention groups (3 SGC and 4 SGCG) were withdrawn. due to a > 3-fold rise above the up-per limit of normal (ULN) in SGPT, which was accom-panied by a mild risein other liver en-zymes and normal serum bilirubin and albumen; three had concealed a past history of chronic compensated hep-atitis (two seropos-itive for hepatitis B virus).

Author / year	Place of study	Study design	Inclusion criteria	Exclusion criteria	Random-ization	Allocation conceal-ment	
Chopra A 2012	Pune India	RCT single blind	Patients of either gender belonging to 17 to 70 years of age and with clinically active (six painful/ tender joints, four swollen joints, and early morning stiffness >30 min) RA [17] were selected. Patients were required to be ambulant (allowed self-support), using analgesic and/ or nonsteroidal anti inflammatory drug (NSAID) for pain relief, not satisfied with the ongoing antiarthritis treatment, and seeking treatment change.	Women who were pregnant or lactating and those having child-bearing potential but not following adequate contraceptive measures; patients with known contraindication to any of the investigational products and medicinal plants; those with other inflammatory arthritis (such as lupus), severe degenerative joint diseases, or other joint diseases which would interfere with the evaluation of RA; patients on any kind of DMARD (including biologic) unless the same had been discontinued at least 2 months prior to the study; those with severe disabling arthritis and/ or incapacitated and bedridden; patients with history of intra-articular knee injection (in particular corticosteroids and hyaluronan equivalents) within the month preceding the study; thosewho were on treatment with anticoagulants, hydantoin, lithium, higher-dose steroids (7.5 mg or more daily prednisolone), colchicine; those with history of active peptic ulcer anytime in the preceding 6 months or bleeding ulcer anytime in the past; patients with evidence of severe unstable renal, hepatic, hemopoietic, and cardiac disorder as revealed by history and/or investigations; those having history of any investigational drug received in the preceding 1 month; those who were unwilling to come for regular follow-up for the entire duration of the study; those with noncooperative attitude; and those who did not justify the inclusion in the opinion of the investigator were excluded	Yes Computer generated	Yes	

	Blinding	Blinding of outcome assess-ment	Treatment arm	Placebo arm	Primary outcome measure	Other outcome measures	Adverse events
	Single blind	No	polyherb (Tinospora cordifolia and Zingiber officinale based) and monoherb (Semecarpus anacardium).	HCQs	Study measures included joint counts (pain/ten-derness and swelling), pain visual analogue scale, global disease as-sessments, and health assessment question-naire.		Epigastria burning Nausea Constipation Itching Dysuria

Author / year	Place of study	Study design	Inclusion criteria	Exclusion criteria	Random-ization	Allocation conceal-ment	
Adhvaryu MR 2008	Gujarat India	Randomized controlled trial	Active pulmonary or extra pulmonary tuberculosis 15 to 85 years	Pregnancy Alcoholism Kidney failure Pre-existing liver disease	Random-ization method and protocol not mentioned	Not mentioned	
Puran-dare H 2007	Mumbai India	Randomized controlled dou-ble-blind trial	Adult patients of either sex with diabetic foot ulcer not less than 4 cm in diameter *Ulcers of Wagner's system's Grade I or Grade II; and digital, ray or forefoot amputations with non-healing ulcer	Patients with ulcer of any other etiology *Patients with local or systemic disease or on therapy that may interfere with wound healing *Ulcer with radiographic evidence of osteomyelitis or involving joint spaces or bones (Wagner's Grade III and IV)	Random-ization done, details not available	Not mentioned	

	Blinding	Blinding of outcome assess-ment	Treatment arm	Placebo arm	Primary outcome measure	Other outcome measures	Adverse events
	Not mentioned	Not mentioned	Curcumin enriched (25%) CL and a hydro-ethanolic extract enriched (50%) TC 1 g each divided in two doses comprised the herbal adjuvant. Plus HRZE	HRZE	Primary end-points were to observe the devel-opment of hepatotoxici-ty in both the groups with assessment of severity by biochemical parameters and liver function tests if the hepatotoxic-ity exceeded Grade Ⅲ parameters.	Secondary outcome was to assess the impact of adjuvant medicine on the outcome of TB itself as defined by follow-up investiga-tions, clini-cal cure and functional vimprove-ment	Nausea vomiting epigastria discomfort
	Yes	Not mentioned	Tinospora cordifolia for 1 month plus optimized medical therapy	Optimized medical ther-apy	Mean ulcer area, depth and perimeter were measured and swabs taken for culture.	None	None mentioned

Author / year	Place of study	Study design	Inclusion criteria	Exclusion criteria	Random-ization	Allocation conceal-ment	
Badar VA 2005	Nagpur India	Randomize double blind place-bo-con-trolled trial	Subjects diagnosed to be suffering from allergic rhinitis. • Volunteering to participate and give signed informed consent. • Of either gender. • In age range of 18–60 years.	Pregnant and lactating women. • Clinical evidence of bacterial sinusitis. • Associated chronic diseases like hypertension, ischemic heart disease, diabetes, psychiatric and CNS disorders. • Consuming concurrent medication for chronic diseases. • Alcoholics and drug addicts. • Having cyanosis, clubbing or lymphadenopathy. • Within 6 weeks of having received antihistaminic or steroidtherapy	Random-ization done, details not available	Not mentioned	

	Blinding	Blinding of outcome assess-ment	Treatment arm	Placebo arm	Primary outcome measure	Other outcome measures	Adverse events
	Double blind, same type of tablets	Not mentioned	300 mg of standardized extract obtained from water extract of stem of TC for 8 weeks	placebo	Sneezing nasal discharge Nasal obstruction Nasal pruritis	None	No severe adverse events reported

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Technical Dossier on

Guduchi

(Tinospora cordifolia)

Technical Dossier on Guduchi

(Tinospora cordifolia)

The safety of Guduchi (Tinospora cordifolia) can be inferred from the efficacy-related clinical studies where no adverse effects are reported. The data on its widespread use globally as well as in folklore medicine with other medications or stand-alone also could throw light on its safety in diverse clinical contexts.

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