How to Cite:
Singh, R., & Sharma, L. (2022). Potential role of tinospora cordifolia in management of COVID-19: A systematic review. *International Journal of Health Sciences*, *6*(S5), 10597–10608.
https://doi.org/10.53730/ijhs.v6nS5.10812

Potential role of tinospora cordifolia in management of COVID-19: A systematic review

Richa Singh
Assistant Professor and Research Scholar, Department of Dietetics & Applied Nutrition, Amity Medical School, Amity University Haryana, India
Email: richasingh.karma@gmail.com ; rsingh1@ggn.amity.edu
https://orcid.org/0000-0003-3717-8219

Dr. Luxita Sharma
Associate Professor & Head Amity Medical School, Department of Dietetics & Applied Nutrition, Amity Medical School, Amity University Haryana, India
Email: lakshita1982@gmail.com ; lshrama@ggn.amity.edu
https://orcid.org/0000-0002-4700-4792

Abstract*---Background: Tinospora cordifolia*** has gained popularity as an immunomodulatory and protective herb. Being anIndian traditional herb, it has found its use in Ayurveda and alternative system of medicine. According to World Health Organization, still 80% of the world population relies on alternative therapies for disease and infirmity. Dearth of medicine and treatment for COVID-19 has pushed researcher towards alternative therapies. This review focuses on the potential role of *T.cordifolia* in management of Coronavirus disease. *Methods:*A systematic review has been carried out by searching Google Scholar and SCOPUS Database from the year 2020 onwards. The review is written following the PRISMA Guidelines. *Results:*A total of 20 studies have been included in the systematic review. These studies are mainly based on molecular docking (in-silico studies), narrative reviews, retrospective studies, animal experimentation and randomized controlled trials. All the studies reported promising results. *In silico* studies covered the activity of phytochemicals in *T.cordifolia* and their inhibitory action on viral replication and binding. The experimental studies also showed positive results in human as well as animal models. *Conclusion:* Despite the fact that the herb yields positive results in controlling the activity of the virus *in silico* or improvement in the disease conditions in human subjects, but still, advanced *in-vitro* and *in-vivo* studies are required to propose *T.cordifolia* in the line of treatment for COVID-19.

***Keywords*---**Phytochemicals, *in silico* studies, COVID 19.

Background

The entire world is still gripped under the shackles of the deadly Coronavirus. The outbreak of COVID-19 has shaken the foundation of every sphere of life. The inception of the pandemic began from the Wuhan city of the Hubei province of China spreading over 230 countries of the World[1]. The viral illness was declared a pandemic by the World Health Organization in March 2020 and is caused by the "novel coronavirus" – Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The nature of SARS-CoV-2 is similar to SARS-CoV and also presents 79.5% matching genome sequence[2-4]. The virus belongs to the family Coronaviridae and can severely affect the respiratory system. Also, other vital organs belonging to the enteric, hepatic and neurological system are at potential risk, if timely treatment is not initiated. It has been documented that the virus appears to be causing mild to moderate illness in 80% of the infected patients but can be fatal for people with related comorbidities like hypertension, diabetes, cardiovascular disease etc. The fatality rate is around 2.3% [5-7].

As per a report from the Coronavirus Resource Center, John Hopkins University, the tally of confirmed COVID-19 cases in July 2020 reached 13,683,743. The graph of this viral illness has been on the rise, owing to the fact, the illness was declared a pandemic. The symptoms of COVID-19 include some common manifestations in the form of fever, dry cough, shortness of breath etc. In certain cases, some uncommon symptoms liked anosmia, ageusia, diarrhea, tiredness, fatigues, chills, headache, etc can also be seen. Increased fatality might result after development of conditions like pneumonia[8,9]. The mode of infection is through respiratory droplets which may spread through coughing and sneezing by the infected person.

A virus requires host to function. The entry of virus in host's body and further replication is based on genomic encoding of a number of structural and non-structural proteins. The blatant respiratory symptoms are owing to the fact that the viral structure has crown like proteins on its surface which are also called as spike proteins. These spike proteins have a direct affinity to human proteins present inside the nose and endothelial cells of the lungs. Binding together of the spike proteins of the virus with human proteins leads to engulfment of the virus in the human body, followed by replication of the viral DNA and related consequences. The series of consequences include damage to the lungs, heart, brain cells and also other organs[11].

The severe implications of the disease have pushed researcher over the world to find a possible solution to the problem. The virus has burdened the healthcare system, which further aggravated the use and development of the alternative system of medicine. The alternative therapies have more of a preventive and supportive role which might be fruitful in alleviating symptoms and also averting organ damage[10].

In the present time, although vaccines have been developed, but the upcoming mutated strains of the virus which are more contagious still pose a risk on the population. Tinospora cordifolia, also known as Giloy or Guduchi is a traditional Indian herb, which belongs to the family Menispermaceae. It has been known to

possess anti-inflammatory, immunomodulatory, cardioprotective, anti-oxidant, antimicrobial, antidiabetic and anti-carcinogenic properties[12,13]. This review is focused on assessing the role of Tinospora cordifolia in management of COVID-19 and also includes the activities of various compounds of Giloy which might be fruitful in yielding promising results as antiviral composites.

Methods

Study Protocol

We have included all scientific papers- including reviews and research articles which included the role of Tinospora cordifolia in management of COVID-19. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[14]have been followed for the study design, search strategy, screening and reporting, which is supported by the flow diagram depicted in Figure 1. Database searching, selection of studies, evaluation of the quality of studies and extraction of data has been done by both the researchers.

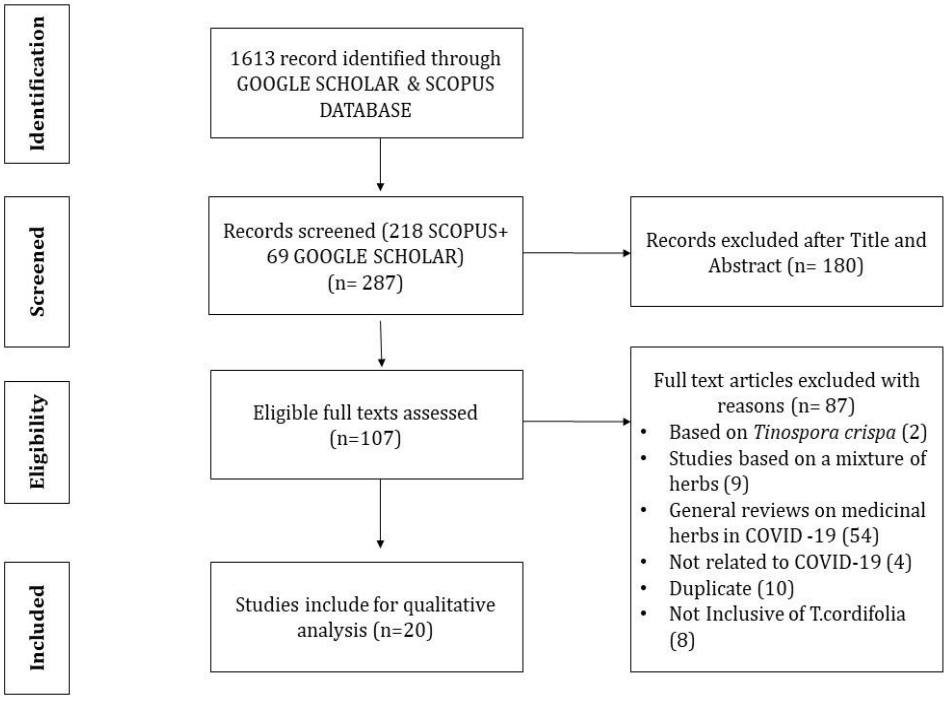

Figure 1 PRISMA Flow Diagram for Systematic Analysis

Inclusion & Exclusion Criteria

Inclusion criteria for the study were as follows:

1. Research and Review articles (narrative, systematic, comprehensive) involving effects of Tinospora cordifolia on management of COVID-19 have been included in this systematic review.
2. Since, we are especially focusing on COVID-19, therefore reviews and researches published in 2020 and afterwards have been included.

3. Papers published in Journals only have been included in this review.

The Exclusion criteria of the study is:

1. All the studies which includes a combination of herbs along with Tinospora cordifolia have been excluded.
2. We have also excluded letters to editors, book chapter, editorial, conference paper, note, short survey etc.
3. Articles with traditional Chinese medicines have also been excluded from this review.

Information Database and Search Strategy

To carry out this systematic review, the relevant keywords were searched in commonly used and reputed databases: SCOPUS &GOOGLE SCHOLAR from the year 2020. Language was restricted to English and no limitations owing to abstract or full text were imposed. Keywords selection was done basedon Mesh terms using “OR” and “AND” operators andincluded the following terms used in titles, abstracts andkeywords in the SCOPUS database:“Tinospora” AND “Cordifolia” AND “COVID-19” OR “SARSCOV-2” OR “COVID” OR “GILOY” OR “GUDUCHI” OR “PREVENTION” OR “TREATMENT” OR “MANAGEMENT”. While in the GOOGLE SCHOLAR Database, the search string used is as follows: “TINOSPORA CORDIFOLIA IN COVID 19” AND “MANAGEMENT” were used.

Selection of studies and data extraction

Two independent authors did the searching of articles from the above mentioned databases using the mentioned keywords. This search yielded articles 1613 (707 from Scopus database and 906 from Google Scholar database) articles. This was done using proper application of filters for language, publication date, source, type of paper. Careful scrutiny of each articles was carried out independently by both the researchers based on predetermined criteria. Initially, the title and abstract of the article was assessed before finally moving on to reading the full text of the article.

Results & Discussion

The search strategy yielded 287 research articles in total. In all these 287 articles, 218 were in the SCOPUS database while 69 were extracted from GOOGLE SCHOLAR database. Among these studies, the title and abstract were evaluated and the final result received after scrutiny of articles, the number was reduced to 20 articles which excluded any duplication of articles listed initially. These 20 articles were then subjected to careful scrutiny and were fully read by the researchers. After due attention, the review was written on the basis of the articles extracted.

Description of Studies

There are 20 manuscripts which have been reviewed after thorough screening from Google Scholar and SCOPUS database. Amongst these studies, there are 07 Narrative reviews, 07 In-silico studies, 03 randomized control trial, and last but

not the least 3 experimental studies. The purpose of each study has been mentioned in detail in Table 1.

Table 1
Description of Included Articles (n=20)

S.No.	Purpose of the Study	Study Design
1	Phytoconstituents of Tinospora cordifolia, as a potential cure for SARS-CoV 2 infection[8].	*In silico* study
2	Inhibition potential of phytoconstituents of Giloy against viral spike protein and human receptor[15].	*In silico* study
3	Medicinal and Biological properties of Tinospora cordifolia as a potential treatment for COVID-19[16].	Narrative Review
4	Phytocompounds of Giloy against viral protease, surface glycoprotein and RNA polymerase[17].	*In silico* study
5	Efficacy of compound- Tinocordiside against viral binding capacity in COVID-19[18].	Experimental Study
6	Effectiveness and Safety of Guduchi Ghan Vati for Covid-19 Asymptomatic Patients[19].	Retrospective study
7	Inhibitory effect of phytocompounds of Tinospora cordiflia against SARS CoV2[20].	*In silico* study
8	Tinospora cordifolia as an antidote of SARS-CoV-2[21].	*In silico* study
9	Role of Kwath made from Guduchi in combating covid-19[22].	Narrative Review
10	Immunomodulatory properties of Tinospora cordifolia in management of COVID-19[23].	Narrative Review
11	Role of Giloy in reversing viral spike protein induced disease in animal model[24].	Animal Experimentation
12	Immune boosting properties of Tinospora cordifolia in COVID-19[25].	Narrative review
13	Tinospora cordifolia as an ayurvedic drug for COVID-19[26].	Narrative review
14	Immunity booster in covid 19 pandemic disease[27].	Narrative review
15	Immunological effect of giloy in COVID-19[28].	Narrative review
16	Guduchi Ghanavati made from Tinospora cordifolia as a potent prophylaxis for COVID-19[29].	Randomized Controlled Trial
17	Effectiveness of Guduchighan Vati in	Randomized Controlled

	asymptomatic patients suffering from COVID-19[30].	Trial
18	Guduchi Ghan Vati in COVID-19[31].	Prospective Interventional Study
19	Bioactive compounds of Giloy against main protease of SARS-CoV2[32].	*In silico* study
20	Effectiveness of Tinospora cordifolia in treating SARS-CoV-2[33].	*In silico* study

Inhibitory activity of phytoconstituents of Tinsopsora cordifolia

A number of bioactive compounds belonging to the category of alkaloids, glycosides, steroids, polysaccharides etc. are present in Giloy. A number of In-silico experiments have been conducted in the recent times to study these bioactive molecules and their possible effect on SARS-CoV-2 virus. A comprehensive literature has been explored here.

In an in-silico study conducted by P. Chowdhury (2021), a number of compounds extracted from Tinospora have been studied for their inhibitory activity. A number compounds like Tetrahydropalmatine, berberine, octacosanol choline and Beta sitosterol were studied. It was found that berberine had a higher affinity to control viral replication and the main protease of the virus[8]. In a similar kind of study, the various constituents of *T.cordifolia* have been examined through pharmacokinetics and molecular docking techniques. The inhibitory effect of several constituents on human ACE2 protein and main protease of the virus has been studied[15]. Another In-silico experiment showed promising results of the natural constituents of Giloy like berberine, isocolumbin, magnoflorine and tinocordiside on viral binding capacity and replication. These constituents possessed greater binding efficacy against SARS-CoV-2 targets (6VSB, 6M0J, 6M71 and 6Y84) involved in attachment and replication of the virus. Here, 6VSBand 6M0J indicate surface glycoproteins while 6M71 indicatesRNA dependent RNA polymerase and 6Y84 is the main protease of the virus [17, 34].

Tinocordiside- a potent phytocompound of *T.cordifolia* has been shown to have a viable affinity for controlling the contamination ability of the SARS-Cov-2 and its entry into host cells. The receptor binding domain (RBD) of the virus on its spike proteins binds to the ACE2 receptors of the host and thus creating a series of interactions between the virus and the host. Tinocordiside inhibits this binding by interrupting electrostatic interactions between host and the virus[11,18]. Another compound Tinosponone has been studied and found to be a strong inhibitor of the main protease of the virus i.e. SARS-Cov-2. Apart from this, compounds like berberine, cardiofolioside B, xanosporic acid were also found to be useful[20]. Similar study conducted by Thakkar et al., 2021 showed the secondary metabolites of *T.cordifolia* having higher potency to inhibit the main protease of SARS-CoV-2[21]. Cordifolioside can be used in the treatment of COVID-19 as per an in-silico study conducted by Manne et al., 2021. This compound has immunomodulatory effect on human TGF-β and TNF-α along with being an inhibitor to the viral protease[32]. Similar results have been reported by Badri et al., 2021, where the bioactives of the traditional herb *T.cordifolia* can

successfullyweaken the entry and replication of viral proteins by inhibiting the functions specific proteins[33].
All these mentioned In-silico studies are an attempt to find a possible solution for the treatment and prevention of coronavirus disease. Advanced investigations in-vivo and in-vitro will further strengthen the profound efficacy of the bioactives of Tinospora.

Immunomodulatory Properties of *T.cordifolia*

Giloy or Tinospora is an Indian traditional herb which is a potent immunomodulator. Owing to this property, it is also called as *Rasayan Dravya* which means Immunomodulatory Drug[23]. Its effect has been well documented in various common and inflammatory diseases like jaundice, rheumatism, allergies, diabetes etc.[35]The onset of COVID-19 brings along with it a "cytokine storm" caused as a result of increased levels of pro-inflammatory cytokines and chemokines in plasma. This cytokine storm is mainly responsible for severity of the disease and its effect on other organs leading to further complications[36]. Alternation of immune response and disturbance in immune homeostasis are classical features of COVID-19 which can be benefitted with administration of Giloy. The immunomodulatory activities of this herb are also well documented in several studies, one such being an *in-vivo* study on CCl4 intoxicated rats[37].
Specific bioactive compounds of *T.cordifolia* like 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain and syringing have been known to possess immune modulating and cytotoxic properties[26,38].

Ayurvedic Preparationsfrom *T.cordifolia* and their potency in COVID-19

The effect of Guduchi Ghan vati – an Ayurvedic preparation was tested on asymptomatic COVID-19 patients between the age group of 18-75 years were administered the tablet orally in the dose of 1000mg daily for a period of two weeks. This was done in a retrospective study. The results showed faster virologic clearance in patients receiving Ayurveda treatment as compared to the patients on normal allopathic treatment. Also no side-effects of the preparation were reported[30]. Similar study involving the use of Guduchi Ghan Vati involved administration of 1000 mg of tablet twice daily for a period of 2 weeks. This study was done on 46 asymptomatic patients suffering from COVID-19. Positive effects of the preparation were evident in 40 patients who completed the 2-week period[39]. Another randomized controlled pilot study involved administration of Guduchi Ghan Vati in the dosage of 500mg for a period of 10 days against administration of hydroxychloroquine to another group of patients (Control group). The result showed 93.3% participants turned RT-PCR negative for COVID-19 in the intervention group, as compared to 66.6% participants in control group till 10th day of the study period[29].Similar kind of study conducted in a community setting in Hiamchal Pradesh also reported prophylactic properties of Guduchi Ghan Vati without any side effects[31].

Review article by Ansary and Sudhikumar, 2020 has showed promising properties of Guduchyadi Kwatham, which is primarily prepared from Tinospora cordifolia along with some other medicinal herbs. The preparation has been known to be benficial for the respiratory system, gastrointestinal system,Plasma andLymphatic

system, cardiovascular system and also the muscle and adipose tissue[22]. Role of another Ayurvedic preparation –Amritadi Kwath has been outlined in an experimental study by Mishra, 2020. Amritadi kwath is an extract mainly prepared from Tinospora cordifolia along with Withania somnifera, Occimum sanctum and other ingredients[28]. Although this is a retrospective study, which can be carried forward for a randomized control trial. Balkrishna et al., 2021 tested the aqueous extract of *T.cordifolia* on animal model (zebrafish). Administration of the extract lead to reversal of renal necrosis and inflammation in the test animal[24].

Discussion

Tinospora cordifolia is a traditional herb which has been used extensively in the treatment of a number of diseases ranging from jaundice, fever, asthma, diarrhoes, skin diseases etc [40]. This medicinal plant holds a special place in Ayurveda and renowned texts related to it. Ayurveda has regarded this plant as a rasayana, which means a drug having therapeutic benefits. The onset of COVID-19 has regenerated the use of alternative system of medicine for the treatment of this gripping disease which has become a pandemic. The literature reviewed in this manuscript shows the potentiality of *T.cordifolia* in relation to COVID-19.

The plant contains a number of bioactive compounds belonging to the category of alkaloids, glycosides, phenolic compounds, aliphatic compounds,diterpenoids, sesquiterpenoid and various polysaccharides[41]. *In silico* studies involving molecular docking have reviewed the role of a number of phytoconstituents of *T.cordifolia*. These compounds have been tested for their inhibitory properties against viral binding to the host cells. The activity of berberine and tinosponone has been reported to control viral replication and also work on the main protease of the virus. Similar results have been retrieved in testing another bioactive i.e Cordifolioside. Tinocordiside on the other hampers the electrostatic interactions between the viral spike protein and human ACE2 receptor protein. These In-silico studies acts as a base for the further investigations which can be done *in-vitro* and *in-vivo*. Hence, the findings of In-silico studies cannot be regarded as a full-fledged therapeutic cure for COVID-19.

A plethora of articles have reviewed the immunomodulatory properties of *T.cordifolia* which is further supported with a strong research done on human and animal models. Enhanced phagocytic activity and increased action of neutrophils have been manifested in a study involving rats induced with E. coli in intraperitoneal region and then administered plant extract[42]. A wide stream of compounds of giloy have immune modulating activity and these have been discussed in the literature. Ayurvedic preparations like Amritadi Kwath, Guduchi Ghan Vati, Gudichyadi Kwatham have also been studied for their beneficial role in management of COVID-19. But a number of studies in this direction are retrospective and require controlled trials to ensure the efficacy of these preparations in the recovery of patients suffering from SARS-CoV-2 infection.

Conclusion

The systematic review draws attention on the possible researches conducted in the duration of the current pandemic for the alleviation of symptoms and recovery related to COVID-19. While molecular docking studies show promising results, an intensive research based on human/ animal model requires attention in order to label Tinospora cordifolia as a potential cure for COVID-19.

References

1. Adhikari B, Marasini BP, Rayamajhee B, Bhattarai BR, Lamichhane G, Khadayat K, Adhikari, A, Khanal S, & Parajuli N. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review. Phytotherapy research. 2021: 35(3), 1298–1312. https://doi.org/10.1002/ptr.6893
2. Ansary PY and Sudhikumar. KB. Pharmacological Potential of Guduchyadi Kwatham in Combating COVID-19. International Journal of Ayurveda and Pharma Research. 2020;8(6):9-22.
3. Badri K, Aramgam S, et al. Efficacy of Tinospora cordifolia in treating SARS-CoV-2: *in silico* studies. The FASEB Journal. 2021: 35. https://doi.org/10.1096/fasebj.2021.35.S1.04976
4. Balkrishna A, Khandrika L, Varshney A. Giloy Ghanvati (Tinospora cordifolia (Willd.) Hook. f. and Thomson) Reversed SARS-CoV-2 Viral Spike-Protein Induced Disease Phenotype in the Xenotransplant Model of Humanized Zebrafish. Front Pharmacol. 2021;12:635510. Published 2021 Apr 19. doi:10.3389/fphar.2021.635510
5. Balkrishna A, Pokhrel S, Varshney A. Tinocordiside from Tinospora cordifolia (Giloy) May Curb SARS-CoV-2 Contagion by Disrupting the Electrostatic Interactions between Host ACE2 and Viral S-Protein Receptor Binding Domain. Comb Chem High Throughput Screen. 2021;24(10):1795-1802. doi:10.2174/1386207323666201110152615
6. Bharathi C, Aswartha HR, et al. A Review on Medicinal Properties of Tinospora cordifolia. International Journal of Scientific Research and Review. 2018.
7. Bishayi B, Roychowdhury S, Ghosh S, Sengupta M. Hepatoprotective and immunomodulatory properties of Tinospora cordifolia in CCl4 intoxicated mature albino rats. J Toxicol Sci. 2002;27(3):139-146. doi:10.2131/jts.27.139
8. Chen Y, Liu Q & Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. Journal of medical virology. 2020: 92(4), 418–423. https://doi.org/10.1002/jmv.25681
9. Chowdhury P. *In silico* investigation of phytoconstituents from Indian medicinal herb 'Tinospora cordifolia (giloy)' against SARS-CoV-2 (COVID-19) by molecular dynamics approach. Journal of biomolecular structure& dynamics. 2021: 39(17), 6792–6809. https://doi.org/10.1080/07391102.2020.1803968
10. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus:

classifying 2019-nCoV and naming it SARS-CoV-2. Nat Micro. 2020;5: 536–544.
11. Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Le infezioni in medicina. 2020;28(suppl 1):6–17.
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. Lancet. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
13. Jena S, Munusami P, Mm B, Chanda K. Computationally approached inhibition potential of Tinospora cordifolia towards COVID-19 targets [published online ahead of print, 2021 Mar 20]. Virusdisease. 2021;32(1):1-13. doi:10.1007/s13337-021-00666-7
14. Jin Z, Du X, Xu Y, et al. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature. 2020;582(7811):289-293. doi:10.1038/s41586-020-2223-y
15. Kavita V, Anubha C, et al. An Open label prospective interventional study to assess the prophylactic effect of Guduchi Ghan Vati in COVID-19: A community-based study in a containment zone of Himachal Pradesh, India. 2021. https://doi.org/10.31219/osf.io/8vwsy
16. Khan Mujahid and Rathi Bharat. Tinospora Cordifolia-An immunomodulatory drug in Ayurveda for prevention and treatment of Covid-19. International Journal of Research in Pharmaceutical Sciences. 2020: 11, 1695-1699. 10.26452/ijrps.v11iSPL1.4194.
17. Krupanidhi S, Abraham Peele K, Venkateswarulu TC, et al. Screening of phytochemical compounds of Tinospora cordifolia for their inhibitory activity on SARS-CoV-2: an *in silico* study. J Biomol Struct Dyn. 2021;39(15):5799-5803. doi:10.1080/07391102.2020.1787226
18. Kumar Abhimanyu & Prasad Govind, et al. A Retrospective Study on Efficacy and Safety of Guduchi Ghan Vati for Covid-19 Asymptomatic Patients. MedRXIV. 2020. 10.1101/2020.07.23.20160424.
19. Kumar Abhimanyu, Prasad Govind, et al. Efficacy and Safety of Guduchi Ghan Vati in the Management of Asymptomatic COVID-19 Infection: An Open Label Feasibility Study. 2020. 10.1101/2020.09.20.20198515.
20. Manne M, Goudar G, Varikasuvu SR, et al. Cordifolioside: potent inhibitor against Mpro of SARS-CoV-2 and immunomodulatory through human TGF-β and TNF-α. 3 Biotech. 2021;11(3):136. doi:10.1007/s13205-021-02685-z
21. Merta, I. N., & Suderana, I. W. (2020). COVID-19 pandemic handling community social and cultural sector stimulus efforts. International Journal of Social Sciences and Humanities, 4(3), 1–12. https://doi.org/10.29332/ijssh.v4n3.434
22. Mishra B. Immunological effect of Amritadi Kwath for improving immunity to fight covid -19 pandemic. World Journal of Pharmaceutical Research. 2020. Volume 9:9. 1070-1080.
23. Modi B & Shah K, et al. Morphology, Biological Activity, Chemical Composition, and Medicinal Value of Tinospora Cordifolia (willd.) Miers. Advanced Journal of Chemistry. 2020. 10.22034/ajcb.2020.243751.1058.

24. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. Published 2015 Jan 1. doi:10.1186/2046-4053-4-1
25. Murugesan S, Kottekad S, Crasta I, Sreevathsan S, Usharani D, Perumal MK, & Mudliar S N. Targeting COVID-19 (SARS-CoV-2) main protease through active phytocompounds of ayurvedic medicinal plants - Emblica officinalis (Amla), Phyllanthus niruri Linn. (Bhumi Amla) and Tinospora cordifolia (Giloy) - A molecular docking and simulation study. Computers in biology and medicine. 2021:136, 104683. https://doi.org/10.1016/j.compbiomed.2021.104683
26. Patil AM, Gothert JR, Khairnar V. Emergence, transmission, and potential therapeutic targets for the COVID-19 pandemic associated with the SARS-CoV-2. Cellul Physiol Biochem Int J Exp Cellula Physiol Biochem Pharmacol. 2020;54(4):767–90. https://doi.org/10.33594/000000254.
27. Rodríguez-Morales AJ, MacGregor K, Kanagarajah S., Patel D, & Schlagenhauf, P. Going global – Travel and the 2019 novel coronavirus. Travel Medicine and Infectious Disease. 2020: 33. 101578. https://doi.org/10.1016/j.tmaid.2020.101578
28. Sagar Vasanthkumar & Kumar Arun. Efficacy of Natural Compounds from Tinospora cordifolia Against SARS-CoV-2 Protease, Surface Glycoprotein and RNA Polymerase. Biology, Engineering, Medicine and Science Reports. 2020: 6, 6-8. 10.5530/bems.6.1.2.
29. Sanjeev Rastogi, Deep Narayan Pandey, Ram Harsh Singh. COVID-19 pandemic: A pragmatic plan for ayurveda intervention. Journal of Ayurveda and Integrative Medicine. 2020. ISSN 0975-9476, https://doi.org/10.1016/j.jaim.2020.04.002.
30. Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active compounds from Tinospora cordifolia. J Ethnopharmacol. 2012;141(3):918-926. doi:10.1016/j.jep.2012.03.027
31. Shukla U, Ujjaliya N, et al. Efficacy and safety of Guduchighan Vati in asymptomatic and mild to moderate cases of COVID-19: A randomized controlled pilot study. Medrixv. 2021. https://doi.org/10.31219/osf.io/c8f9h
32. Sinaei R, Pezeshki S, Parvaresh S, Sinaei R. Why COVID-19 is less frequent and severe in children: a narrative review. World J Pediatr. 2020;17(1):10-20. doi:10.1007/s12519-020-00392-y
33. Singh A, Singh RS, Sarma P, Batra G, Joshi R, Kaur H, et al. A comprehensive review of animal models for coronaviruses: SARS-CoV-2, SARS-CoV, and MERS-CoV. Virol Sin. 2020;35(3):290–304. https://doi.org/10.1007/s12250-020-00252-z
34. Singh MP. Giloy as immunity booster in COVID 19 pandemic disease. World Journal of Pharmaceutical Research. 2020. Volume 9: 15. 1065-1078.
35. Singh R. Giloy (Tinospora cordifolia): exploring its therapeutic potential. International Journal of Research and Analytical Reviews. 2019:2, 988-995.
36. Sonkamble V and Kamble H. Antidiabetic potential and identification of phytochemicals from Tinospora cordifolia. American Journal of Phytomedicine and Clinical Therapeutics. 2015. 97–110.
37. Sonkamble VV& Kamble LH. Antidiabetic potential and identification of phytochemicals from Tinospora cordifolia. American Journal of Phytomedicine and Clinical Therapeutics. 2015:3, 97–110.

38. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). The COVID-19 pandemic. International Journal of Health Sciences, 5(2), vi-ix. https://doi.org/10.53730/ijhs.v5n2.2937
39. Thakar Anup, Panara Kalpesh,et al. Guduchi Ghanavati to Improve Immune Status and General Health in the Population at High Risk of COVID-19: Results of An Open-Label Non-Randomized Clinical Trial from India. 2021. Available at SSRN: https://ssrn.com/abstract=3798254 or http://dx.doi.org/10.2139/ssrn.3798254
40. Thakkar SS, Shelat F and Thakor P. Magical bullets from an indigenous Indian medicinal plant Tinospora cordifolia: An *in silico* approach for the antidote of SARS-CoV-2. Egyptian Journal of Petroleum. 2021: 30(1), 53–66. https://doi.org/10.1016/j.ejpe.2021.02.005
41. Thatte UM, Rao SG and Dahanukar SA. Tinospora cordifolia induces colony stimulating activity in serum. Journal of Postgraduate Medicine. 1994, 40: 202- 203.
42. Thorat V, Tamboli FA, Jadhav A, Gaikwad R and Rangari D. Role of Tinospora cordifolia as immune booster current covid -19 pandemic. Int J Pharmacognosy. 2020; 8(8): 307-15. http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.8(8).307-15.
43. Varpe SP, Balme VS, et al. Tinospora cordifolia-an immunomodulatory drug in ayurveda for prevention and treatment of COVID-19 and diverse pharmacological importance. World Journal of Pharmaceutical Research. 2021. Volume 10:6. 1734-1747.
44. Widjaja, G. (2021). Impact of human resource management on health workers during pandemics COVID-19: systematic review. International Journal of Health & Medical Sciences, 4(1), 61-68. https://doi.org/10.31295/ijhms.v4n1.850
45. Yang Z, Lasker K, Schneidman-Duhovny D, et al. UCSF Chimera, MODELLER, and IMP: an integrated modeling system. J Struct Biol. 2012. 179;(3). 269-78.