

A CRITICAL REVIEW OF AYURVEDIC DRUGS USED IN COVID-19

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ABSTRACT

The Coronavirus disease 2019 (COVID-19) is triggered by unadorned acute respiratory syndrome Coronavirus-2 (SARS CoV-2) infection attacking mainly on the immune system of a body. It is a possibly fatal disease that is of public health and economy disquiet globally. In December 2019, COVID-19 outburst occurred in Wuhan city, China furthermore spread worldwide. The patients with unembellished diseases may die due to acute respiratory distress syndrome (ARDS) caused by systemic inflammatory antiphons due to the excessive release of pro-inflammatory cytokines and chemokines by the immune effect or cells. In India too, it is spreading very rapidly, although the case fatality rate is below 1.50% ([https:// www. statist a.com](https://www.statista.com)), which is markedly less than in other countries, despite the dense population and minimal health infrastructure in rural areas. Here is an urgent need to find a specific cure for the disease and global efforts are directed at developing SARS-CoV-2 specific antivirals and immune-modulators. Ayurvedic Rasayana therapy has been traditionally used in India for its immunomodulatory and adaptogenic effects, and more recently has been included as therapeutic adjuvant for several maladies. Health promotion, immune-modulation, prevention and reduce disease burden from COVID-19. Drugs such as Ashwagandha (*Withania somnifera* (L.) Dunal), Guduchi (*Tinospora cordifolia* (Willd.) Miers), Amalaki (*Phyllanthus emblica* L.), Mulethi (*Glycyrrhiza glabra* L.), Shatavari (*Asparagus racemosus* Willd.), Chireta (*Andrographis paniculata* (Burm.f.) Nees), Tulsi (*Ocimum sanctum* L.) Punarnava (*Boerhaavia diffusa* L.) and Pippali (*Piper longum* L.) For symptom management of COVID-19 like illness Agastya Haritaki, Anutaila, AYUSH-64 can be used. Scientific research on these drugs may reveal the new approach for the prevention and management of COVID-19. The main aim of this article is to review research which has already conducted and currently being carried out on the herbal plant for their immunomodulation property which have a possible application in the prevention and treatment of COVID-19.

KEYWORDS: Ayurvedic drugs, *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Guduchi), *Asparagus racemosus* (Shatavari), AYUSH 64, Chireta (*Andrographis paniculata* (Burm.f.) Nees), Tulsi (*Ocimum sanctum* L.) Punarnava (*Boerhaavia diffusa* L.) and Pippali (*Piper longum* L.), Ayurveda, COVID-19, SARS-CoV-2.

INTRODUCTION

A worldwide outbreak of severe acute respiratory syndrome coronavirus 2 (SARS - CoV- 2) and the resulting COVID-19 cases and fatalities has challenged health systems globally. Globally, a total of 125 million cases including 2.7 million deaths have been reported by March 25, 2021.^[1] Most of the patients with SARS-Cov-2 infection develop a mild illness, approximately 14 % develop a severe disease that requires hospitalization and oxygen support, and 5 % require admission to an intensive care unit.^[2] As of now, mainly symptomatic supportive treatment is being provided to the patients whereas seriously ill individuals are treated with organ support.^[3] The drug discovery process is accelerated at the moment with much focus on repurposing existing drugs.^[4] The majority of the drugs used for treatment worldwide fall primarily under antiviral, antimalarial, anti-inflammatory, monoclonal

antibodies. Coronaviruses (CoVs) are large viruses comprising of four genera, namely alpha, beta, gamma, and delta. The betacoronavirus class includes severe acute respiratory syndrome (SARS) virus (SARS-CoV), Middle East respiratory syndrome (MERS) virus (MERS-CoV), and the COVID-19 causative agent SARS-CoV-2. (Li G. et al., 2020). The novel SARS-CoV-2 is a beta CoV that shows 88% similarity to two bat-derived SARS-like CoVs (bat-SLCoVZC45 and bat-SL-CoVZXC21), about 50% identical to the sequence of MERS-CoV, and 70% similarity in genetic sequence to SARS-CoV (Cheng and Shan, 2020). Although there is an extremely high resemblance between SARS-CoV and the novel SARS-CoV-2, the SARS-CoV-2 is spreading rapidly as compared to the SARS-CoV, which may be explained by structural differences in the S-proteins (Rabaan et al., 2020). The SARS-CoV-2 S protein has been found as a significant determinant of virus entry

into host cells using angiotensin converting enzyme 2 (ACE2) receptor similar to SARS-CoV. Whereas the binding affinity of virion S glycoprotein and ACE2 is reported to be 10–20 folds higher in SARS-CoV-2 as compared to that of SARS-CoV (Song et al., 2018). The concept of pandemic disease is mentioned by Acharya Charaka in Janapadodhwansa Chapter 3rd in Vimana sthana. Acharya Charaka explained that Vayu (air), Jala (water), Desh (soil & area) and Kala (time) are four responsible factors for group infection in the community and further described the whole concept of managing pandemic situation⁵. For any epidemic condition Panchakarma (five procedures of purification), Rasayana Chikitsa (immune-modulators therapy) and Sadvritta (good conduct) are leading treatments in Ayurveda.^[5] Among these the foremost treatment is the Rasayana Chikitsa. There are several compounds and herbs having the Rasayana effect. Rasayana drugs enriches the basic Dhatu i.e. Rasa which further resulted in Sapta Dhatus of optimum quality and hence, body, soul and mind gets their nourishment. Rasayana dravyas is mentioned for groups of important drugs that supposed to improve defence mechanism and enhance longevity.^[6] Rasayana may be used in two ways, either as a prophylactic medicine or as a preventive measure in healthy people.^[7] Human immune system is complex and there lies a delicate balance between health and disease. Any substance, synthetic or biological, which can enhance, suppress or modulate the immune system is called an immunomodulator drugs. Till date many of the Rasayana dravyas are known for their immunomodulatory effects via modulation of cytokine secretion, histamine release, immunoglobulin secretion, lymphocyte secretions and phagocytosis and so on⁸. Therefore, Rasayana dravyas such as Ashwagandha (*Withania somnifera* (L.) Dunal), Guduchi (*Tinospora cordifolia* (Willd.) Miers), Amalaki (*Phyllanthus emblica* L.), Mulethi (*Glycyrrhiza glabra* L.), Shatavari (*Asparagus racemosus* Willd.), Chireta (*Andrographis paniculata* (Burm.f.) Nees), Tulsi (*Ocimum sanctum* L.) Punarnava (*Boerhaavia diffusa* L.) Pippali (*Piper longum* L.) and other Ayurvedic measures like Swarna prashana for children can be potential drugs for providing preventive, supportive and rehabilitative care in the treatment of COVID-19 patients by modulating the immune system.

Ayurvedic Drugs used in COVID-19

In the twenty two century the requests of herbal drugs to maintain health and prevention from diseases are attainment immense consideration around the world. According to WHO almost 4 billion people (80%) of the world currently depends on herbal medicine for some aspect of primary health care.^[9] In Ayurveda, Rasayana dravyas are known for their immunomodulation and transformation properties, which may be significant in the preclusion and management of COVID-19. Clinically, immunomodulatory drugs can be categorized into Immunoadjuvant (enrichment of vaccine efficacy), Immunostimulants (improvements of body's immunity through innate as well as adaptive immune responses)

and Immunosuppressants (suppress the immune system in organ transplant and autoimmune diseases).^[10] Numerous Rasayana drugs established the immunomodulatory effects in vitro and clinical revisions such as Ashwagandha (*Withania somnifera* (L.) Dunal), Guduchi (*Tinospora cordifolia* (Willd.) Miers), Amalaki (*Phyllanthus emblica* L.) etc.

Ashwagandha (*Withania somnifera* (L.) Dunal):

Ashwagandha known as Indian winter cherry and Indian ginseng is one of the most significant herbs in Ayurveda and used for the immunomodulation, contesting infectious agents, managing of stress and recovers good physical and mental health. Ashwagandha enriches nitric oxide synthetase activity of the macrophages, which help in refining immune cells. *Withania somnifera* glycoprotein (WSG) is a potent basis of antimicrobial activity.^[11] Ashwagandha helps to reinstate immune homeostasis by providing immune-suppression or immune stimulation effects. Ashwagandha offers anti-viral immunity by aggregate Interferon gamma (IFN γ responses) and anti-inflammatory actions by declining the quantity of Interleukin -1, Interleukin -6 and Tumor necrosis factor which are the main influences related to COVID-19. Ashwagandha may be an effective agent in the management of COVID-19 infection by modulation of host Th-1/Th-2 immunity. Ashwagandha extract gives competent protective immune reactions when added with DPT (Diphtheria, Pertussis, Tetanus) vaccine against fatal outcome of diphtheria and pertussis toxins (30). Ashwagandha helps enrichment of immunogenicity and constructive effect on symptoms in conjunction with anti-tuberculosis drugs used as a directly observed treatment, short-course (DOTS).^[12]

Guduchi (*Tinospora cordifolia* (Willd.) Miers):

Guduchi is one of the best Rasayana and known as "Amrita" means revitalise dead cells and have immunomodulatory and increases innate immunity against COVID-19 infections. Tinosporin, diterpenoid has very effective anti-viral property especially for the treatment of retroviruses and other viral diseases.^[13] Aqueous extracts *T. cordifolia* has subjective the cytokine production and initiation of immune effector cells.^[13] Guduchi is a potent hepato-protective so effective in preventing in hepatotoxicity. It enhances the level of vitamin C and thus functions as an antioxidant.^[14] Guduchi stem has immunomodulatory protein which increases the number of macrophages and its phagocytic activity.^[15] **Sanshamani Vati** (also called Guduchi ghana vati) which encompasses aqueous extract of *T. cordifolia* can be advised as 500 mg twice a day, 15 days with warm water as a preventive and prophylactic drug for COVID-19.^[16]

Amalaki (*Phyllanthus emblica* L.): Amalaki is a rich source of vitamin C (Ascorbic acid)^[17] Acharya Charaka has described that Amalaki is the best rejuvenating herb^[18] and beneficial in relieving cough and skin

diseases.^[19] Amalaki expands both cell mediated and humoral immune response. It enhances IL-2, gamma – IFN and natural killer (NK) cell activity. Amalaki is a well-known drug for its anti-oxidant, detoxification and antiaging activity.^[20] *P. emblica* has an antibacterial effect on Gram-negative and Grampositive organisms due to the presence of flavonoids component. Antimicrobial activity of flavonoids is probably due to the aptitude to form complex with extracellular and soluble proteins, or with bacterial cell walls which dislocates the microbial membranes.^[21] Pulmonary antioxidant defences are widely scattered in lungs and include both enzymatic and non-enzymatic systems. The primary non-enzymatic antioxidants are membrane-bound vitamin C and vitamin E. Amalaki is the richest source of vitamin C.^[22]

Mulethi (*Glycyrrhiza glabra* L.): The major photo components reported in Mulethi (*Yashtimadhu*) is glycyrrhizin which is promising candidates in constraining replication of the SARS associated virus.^[23] Mulethi (*Yashtimadhu*) recovers the resistance against the herpes simplex virus type 1 (HSV-1) by Type I and II interferons (IFN) and Th2 cytokines secretion.^[24] It has antiviral activity against Human immunodeficiency virus (HIV), potent immunomodulatory and antioxidant activity.^[25]

Shatavari (*Asparagus racemosus* Willd.): Shatavari is an important Ayurvedic rejuvenating tonic for the female, as *Ashwagandha* (*Withania somnifera*) for the male. Shatavari has a potent immunomodulatory property by altering the function of macrophages.^[26] It has immunoadjuvant potential with Diphtheria, Tetanus, Pertussis (DPT) vaccine by important up regulation of Th-1, Th-2 and cytokines and immuno stimulation property by important increase of CD4/ CD8 along with T cell activation.^[27]

Kalmegha (*Andrographis paniculata* (Burm. f.) Nees): Kalmegha is a significant Ayurvedic drug which has the capacity to treat viral respiratory infections and augment the immune response. It has viricidal activity against Herpes simplex virus 1 (HSV-1) and HIV by a significant rise in the mean CD4+ lymphocyte level.^[28] *Andrographolides*, the main ingredient of *A. paniculata* improve immune system such as the production of white blood cells, release of interferon and activity of the lymph system. The lymph carries away the by-products of cellular metabolism and acts as a shuttle for invading bacteria and viruses. The wide tissue and organ spreading and the immune-stimulating and regulatory actions of Kalmegha make it an ideal applicant in the prevention and treatment of many diseases and conditions.^[29]

Tulsi (*Ocimum sanctum* L.): Tulsi is regarded as mother medicine of nature and it abridges the course of all illness. Tulsi has antibacterial, anti-viral and anti-fungal activity.^[30] A decoction of the leaves of Tulsi is

valuable for the treatment of respiratory disorders (bronchitis, asthma, influenza, cough and cold)^[31] Flavonoids present in the extracts of Tulsi leaves have been found to be accountable for the immunomodulatory properties by the augmented level of IL-4, natural killer cells and helper cells.^[31] The essential oils like Eugenol of Tulsi leaves yield anti-viral activity against different viruses e.g. polio virus type 3, herpes virus (HSV), hepatitis B virus etc.^[32] Ethanolic extract of Tulsi plant leaves in a range of 22.5 mg/ml attentiveness inhibit repetition of polio type 3 virus. The extracted mechanisms of Tulsi like linalool and ursolic acid has shown broad- spectrum antiviral activity against DNA viruses like RNA virus and adenoviruses.^[33] *Punarnava* (*Boerhaavia diffusa* L.) *Punarnava* has immunomodulatory effects due to its immunosuppressive and immunostimulatory activity.^[34] Administration of *Punarnava* significantly reduced the raised levels of proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6 in mice. These results indicate the immunomodulatory activity of *Punarnava*.^[35] Extracts of *B. diffusa* roots have anti-inflammatory activity by inhibiting natural killer (NK) cell, cytotoxicity, production of nitric oxide in human and very high antiviral activity.^[36] *Pippali* (*Piper longum* L.) *Pippali Rasayana*, a famous Ayurvedic preparation, conveyed having significantly activated macrophages in an experimental study on mice. Administration of *P. longum* extract and its phytochemical piperine augmented the total WBC count, Bone marrow cellularity and α -esterase positive cells in mice.^[37] Immunomodulatory action of *Pippali* fruits (via modulation of both specific and non-specific immune response) has been reported by using macrophage migration index (MMI), haemagglutination titre (HA) and phagocytic index (PI) in mice. The result was more prominent at a lower dose (225 mg/kg) and was marginally reduced when the dose was increased.^[38] *Pippali Rasayana*, a famous Ayurvedic preparation, stated to activating macrophages significantly in mice, infected with *Giardia lamblia* as shown by an increased MMI and phagocytic activity.

CONCLUSION

In this review, Drugs such as *Ashwagandha* (*Withania somnifera* (L.) Dunal), *Guduchi* (*Tinospora cordifolia* (Willd.) Miers), *Amalaki* (*Phyllanthus emblica* L.), *Mulethi* (*Glycyrrhiza glabra* L.), *Shatavari* (*Asparagus racemosus* Willd.), *Chireta* (*Andrographis paniculata* (Burm.f.) Nees), *Tulsi* (*Ocimum sanctum* L.) *Punarnava* (*Boerhaavia diffusa* L.) and *Pippali* (*Piper longum* L.) For symptom management of COVID-19 like illness *Agastya Haritaki*, *Anutaila*, *AYUSH-64* can be used. Scientific research on these drugs may reveal the new approach for the prevention and management of COVID-19.

REFERENCES

1. WHO Coronavirus Disease (COVID-19) Dashboard. Updated March 25, 2021. Accessed March 25, 2021. <https://covid19.who.int/>
2. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China. *China CDC Weekly*, 2020; 2(8): 113-122.
3. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*, 2020; 7(1): 4. doi:10.1186/s40779-020-0233-6.
4. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol*, 2020; 38(4): 379-381. doi:10.1038/d41587-020-00003-1.
5. Pandey Gangasahay, editor. Pt. Kashinath Sastri Vidhyotini Hindi commentator of Charaka Samhita of Agnivesha- 1 st Vol. Viman Sthan chapter 3 verse 8. Varanasi: Chaukumba Sanskrit Sansthan, 2006; 445.
6. Satyapal Singh, Byadgi PS, Tripathi JS, Rai NP. Clinical appraisal of immunomodulators in Ayurveda in the light of recent pharmacological advances. *World J Pharm Res.*, 2015; 4(4): 678-92.
7. Chauhan VP, Dutt B, Vyas M, Gupta SK. Effect of immunomodulators (Rasayana Dravya) in Janapadodhwansa WSR to COVID-19. *J Ayu Herb.*, 2020; 6(1): 26- 29.
8. Kumar VP, Kuttan R, Kuttan G. Effect of “Rasayanas” a herbal drug preparation on cell mediated immune responses in tumor bearing mice. *Indian J Exp Biol*, 1999; 37(1): 23-26.
9. Hashemi SR, Davoodi H. Herbal plants as new immunostimulator in poultry industry: a review. *Asian Journal of Animal and Veterinary Advances*, 2012; 7(2): 105-16. <https://doi.org/10.3923/ajava.2012.105.116>.
10. Mahima , Anu Rahal, Rajib Deb, Shyma K. Latheef, Hari Abdul Samad, et al. Immunomodulatory and Therapeutic Potentials of Herbal, Traditional/Indigenous and Ethnoveterinary Medicines. *Pakistan Journal of Biological Sciences*, 2012; 15(16): 754-74. <https://doi.org/10.3923/pjbs.2012.754.774>
11. Tiwari R, Chakraborty S, Saminathan M, Dhama K, Singh SV. Ashwagandha (*Withania somnifera*): Role in safeguarding health, immunomodulatory effects, combating infections and therapeutic applications: A review. *Journal of Biological Sciences*, 2014; 14(2): 77-94. <https://doi.org/10.3923/jbs.2014.77.94>
12. Gautam M, Diwanay SS, Gairola S, Shinde YS, Jadhav SS, Patwardhan BK. Immune response modulation to DPT vaccine by aqueous extract of *Withania somnifera* in experimental system. *International immunopharmacology*, 2004; 4(6): 841-9. <https://doi.org/10.1016/j.intimp.2004.03.005>
13. Kumar R, Rai J, Kajal NC, Devi P. Comparative study of effect of *Withania somnifera* as an adjuvant to DOTS in patients of newly diagnosed sputum smear positive pulmonary tuberculosis. *Indian Journal of Tuberculosis*, 2018; 65(3): 246- 51. <https://doi.org/10.1016/j.ijtb.2017.05.005>.
14. Akhtar S. Use of *Tinospora cordifolia* in HIV infection. *Indian Journal of Pharmacology*, 2010; 42(1): 57. <https://doi.org/10.4103/0253-7613.62402>.
15. Upadhyaya R, Pandey RP, Sharma V, Verma Anita K. Assessment of the multifaceted immunomodulatory potential of the aqueous extract of *Tinospora cordifolia*. *Research Journal of Chemical Sciences*, 2011; 1(6): 71-79.
15. Mainzen Prince PS, Padmanabhan M, Menon VP. Restoration of antioxidant defence by ethanolic *Tinospora cordifolia* root extract in alloxan induced diabetic liver and kidney.- *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, 2004; 18(9): 785-87. <https://doi.org/10.1002/ptr.1567>
16. Aranha I, Clement F, Venkatesh YP. Immunostimulatory properties of the major protein from the stem of the Ayurvedic medicinal herb, guduchi (*Tinospora cordifolia*). *Journal of ethnopharmacology*, 2012; 139(2): 366-72. <https://doi.org/10.1016/j.jep.2011.11.013>.
17. Ministry of AYUSH, Advisory from ministry of Ayush for meeting the challenge arising out of spread of corona virus (COVID-19) in India, 2020. Available from: <https://www.ayush.gov.in/docs/125.pdf>
18. Pandey Gangasahay (editor). Pt. Kashinath Sastri Vidhyotini Hindi commentator of Charaka Samhita of Agnivesha- 1st volume, Sutra Sthan chapter 25 verse 40. Varanasi: Chaukumba Sanskrit Sansthan, 2006; 201.
19. Pandey Gangasahay, editor. Pt. Kashinath Sastri Vidhyotini Hindi commentator of Charaka Samhita of Agnivesha- 1st volume, Sutra Sthan chapter 4 verse 11-13. Varanasi: Chaukumba Sanskrit Sansthan, 2006; 88.
20. Sharma R, Martins N, Kuca K, Chaudhary A, Kabra A, Rao MM, Prajapati PK. Chyawanprash: A traditional Indian bioactive health supplement. *Biomolecules*, 2019; 9(5): 161. <https://doi.org/10.3390/biom9050161>
21. Saini A, Sharma S, Chhibber S. Protective efficacy of *Emblca officinalis* against *Klebsiella pneumoniae* induced pneumonia in mice. *Indian Journal of Medical Research*, 2008; 128(2): 188- 93.
22. Tsuchiya H, Sato M, Miyazaki T, Fujiwara S, Tanigaki S, Ohyama M, Tanaka T, Iinuma M. Comparative study on the antibacterial activity of phytochemical flavanones against methicillin-resistant *Staphylococcus aureus*. *Journal of Ethnopharmacology*, 1996; 50(1): 27-34. [https://doi.org/10.1016/0378-8741\(96\)85514-0](https://doi.org/10.1016/0378-8741(96)85514-0)

23. Repine JE, Bast AA, Lankhorst ID, Oxidative Stress Study Group. Oxidative stress in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, 1997; 156(2): 341-57. <https://doi.org/10.1164/ajrccm.156.2.9611013>
24. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots and replication of SARS-associated coronavirus. *The Lancet*, 2003; 361(9374): 2045-46. [https://doi.org/10.1016/S0140-6736\(03\)13615-X](https://doi.org/10.1016/S0140-6736(03)13615-X)
25. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. *Acta Pharmaceutica Sinica B.*, 2015; 5(4): 310-15. <https://doi.org/10.1016/j.apsb.2015.05.005>.
26. Akamatsu H, Komura J, Asada Y, Niwa Y. Mechanism of antiinflammatory action of glycyrrhizin: effect on neutrophil functions including reactive oxygen species generation. *Planta Medica*, 1991; 57(02): 119-21. <https://doi.org/10.1055/s-2006-960045>
27. Dahanukar S, Thatte U, Pai N, Mose PB, Karandikar SM. Protective effect of *Asparagus racemosus* against induced abdominal sepsis. *Indian Drugs*, 1986; 24(3): 125-28.
28. Gautam M, Diwanay S, Gairola S, Shinde Y, Patki P, Patwardhan B. Immunoadjuvant potential of *Asparagus racemosus* aqueous extract in experimental system. *Journal of ethnopharmacology*, 2004; 91(2-3): 251-55. <https://doi.org/10.1016/j.jep.2003.12.023>
29. Naik SR, Hule A. Evaluation of immunomodulatory activity of an extract of *andrographolides* from *Andrographis paniculata*. *Planta Medica*, 2009 Jun; 75(08): 785-91. <https://doi.org/10.1055/s-0029-118539>
30. Carr RR, Nahata MC. Complementary and alternative medicine for upper-respiratory-tract infection in children. *American Journal of Health-System Pharmacy*, 2006; 63(1): 33-39. <https://doi.org/10.2146/ajhp040613>.
31. Cohen MM. Tulsi-*Ocimum sanctum*: A herb for all reasons. *Journal of Ayurveda and Integrative Medicine*, 2014; 5(4): 251-33. <https://doi.org/10.4103/0975-9476.146554>.
32. Pattanayak P, Behera P, Das D, Panda SK. *Ocimum sanctum* Linn. A reservoir plant for therapeutic applications: An Overview. *Pharmacognosy Reviews*, 2010; 4(7): 95-105. <https://doi.org/10.4103/0973-7847.65323>.
33. Mondal S, Varma S, Bamola VD, Naik SN, Mirdha BR, Padhi MM, Mehta N, Mahapatra SC. Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (*Ocimum sanctum* Linn.) leaf extract on healthy volunteers. *Journal of Ethnopharmacology*, 2011; 136(3): 452-56. <https://doi.org/10.1016/j.jep.2011.05.012>
34. Ravi V, Parida S, Desai A, Chandramuki A, Gourie Devi M, Grau- GE. Correlation of tumor necrosis factor levels in the serum and cerebrospinal fluid with clinical outcome in Japanese encephalitis patients. *Journal of Medical Virology*, 1997; 51(2): 132-36. [https://doi.org/10.1002/\(SICI\)1096-9071\(199702\)51:2<132::AID-JMV8>3.0.CO;2-8](https://doi.org/10.1002/(SICI)1096-9071(199702)51:2<132::AID-JMV8>3.0.CO;2-8).
35. Sangeetha P, Poornamathy JJ. In vitro assessment of antiinflammatory activity of *Ocimum sanctum* (karunthulasi leaves). *Int Pharma Bio Sci.*, 2015; 6: B1387-91.
36. Mungantiwar AA, Nair AM, Shinde UA, Dikshit VJ, Saraf MN, Thakur VS, et al. Studies on the immunomodulatory effects of *Boerhaavia diffusa* alkaloid fraction. *Journal of Ethnopharmacology*, 1999; 5(2): 125-31. [https://doi.org/10.1016/S0378-8741\(98\)00153-6](https://doi.org/10.1016/S0378-8741(98)00153-6).