https://doi.org/10.47552/ijam.v16i1.5456 ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 16 (1), 2025; 136-141

The Effect of *Kokilaksha Ghanavati* & *Guduchi Ghanavati* in the management of *Vatarakta* (Gout) – A Randomised Clinical Study

Reserach Article

Aarti Gaikar[1], Varghese Jibi[2*], Pooja Kombe[3], Abhilasha Singh[4], Megha Sawle[5], Manna Mathew[6]

1,4,5. PG Scholar, 2. Professor, 3. Assistant Professor
Department of Kayachikitsa, Dr. D.Y. Patil College of Ayurved and Research Centre,
Dr. D. Y Patil Vidyapeeth (Deemed to be University) Pimpri, Pune 411018, Maharashtra, India.
6. Ayurveda Consultant and Dravyaguna expert, Ayur- Arogyam, Nigdi, Pune. India.

Abstract

Background: Amid the joint conditions outlined in the texts of *Ayurveda, Vatarakta* (Gout) is the most common type of inflammatory arthritis; its rising global prevalence is the outcome of rapid modernization and faulty dietary practices, and has a significant detrimental effect on health, quality of life and productivity. Objective: To compare the efficacy of *Kokilaksha Ghanavati* and *Guduchi Ghanavati* in *Vatarakta* (gout). Materials and Methods: The present trial was a randomised clinical study. Computer-generated randomization and participants fufilling the criteria of *vatarakta* symptoms were recruited in two groups. Group A intervened with *Kokilaksha Ghanavati* and Group B with *Guduchi Ghanavati* for 14 days, with follow-up on 7th day and assessed with subjective and objective parameters. Results: The findings of the research revealed that Group B had statistically significant improvement compared to Group A on the *Sandhi shoola* (joint pain)*, sankochan* (stiffness), visual analog scale (VAS) score, while Group A considerably outperformed Group B with regard to improvement in *Sandhi Shotha* (joint swelling). *Daha* (burning sensation)*, sparsha-asahatva* (tenderness) and serum uric acid showed comparable improvements in both the groups. Conclusion: *Guduchi Ghanavati* proved to outscore *Kokilaksha Ghanavati* in the management of *Vatarakta*. However, *Kokilaksha Ghanavati* showed major improvement in key feature of the disease (*shotha*-86.21%), along with visible improvement in other parameters as well. The positive impact of it on *vatarakta* is also undeniable.

Keywords: *Vatarakta,* Gout, Inflammatory arthritis, *Kokilaksha, Guduchi, Ghanavati.*

Introduction

Gout is a type of arthritis (inflammatory disease) that occurs when an excess amount of uric acid concentrates in the blood. Aetiology primarily includes either excessive uric acid production or reduction in uric acid clearance. Uric acid is typically eliminated by urine, which is a byproduct of purine metabolism. *Homo sapiens* lack uricase (urate oxidase), an enzyme that helps in degradation of uric acid into allantoin. The primary underlying cause of gout is hyperuricemia, a condition where monosodium urate (MSU) crystals build up in articular and non-articular structures, and cause pain, swelling and tenderness, including the development of a tophi. Among the treatment of acute attack of gout incorporates NSAIDs, oral colchicine, corticosteroids, ACTH gel, interlukin 1 inhibitors, while in certain indications, urate lowering therapy for which allopurinol, febuxostat, uricosuric agents like probenecid are relied on. In about 90% of patients with gout, develops urate nephropathy or obstructive uropathy. (1)

Studies have indicated that individuals with increased concentration of serum urate levels have higher chance of developing gout, and eventually have more recurrent gout attack over time. Based on documented epidemiological data, excessive protein intake and sedentary lifestyle, these factors are linked to the increasing global burden of gout. (2)

Etiologically and symptomatically, *Vatarakta* and Gout are much alike. Several *Ayurvedic* texts provide a description of *Vatarakta; Charaka* distinguished it as a separate disease, while *Sushruta Samhita* explains it under *mahavatavyadhi chikitsa adhyaya*.(3) The disease *vatarakta* is the outcome of numerous aetiological factors; i.e., faulty dietary habits like *virudhashana* (misconjugation of food), overconsumption of meat, purine-rich food, excessive alcohol intake (in particular beer), altered sleep patterns, *veganigraha* (repression of natural urges) and psychological components such as excessive anger contribute to exacerbation of the disease. (4) The pathology of the illness comprises: Both *vata-rakta* get vitiated. The deranged *rakta* disrupts the *vata's* path, and vitiates *rakta* further,

*** Corresponding Author:**
Varghese Jibi
Professor, Department of Kayachikitsa,
Dr. D. Y. Patil College of Ayurved and Research Centre, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pimpri, Pune 411018, Maharashtra, India
Email Id: vjayu82@gmail.com

resulting in manifestation of the disease. (5) *Vatarakta* can cause a variety of symptoms, like pain & swelling that hinder routine activities.

The disease has had an ascending prevalence in today's time, with a rate of 2.0 to 2.6 per 1000 patients. (6) It is more frequent in males than females. The condition has recurrent flare-ups, which contribute to its chronic nature and its associated complications, which make the disease difficult to treat. *Ayurveda* has the ability to treat the disease effectively and with promising positive outcomes. This research work is intended to compare the effectiveness of single drugs in treating the disease and it will serve as a baseline for further clinical research in *Vatarakta.* Aim: To evaluate the efficacy of *Kokilaksha Ghanavati* and *Guduchi Ghanavati* in *Vatarakta* (Gout) Objective: To compare the efficacy of *Kokilaksha Ghanavati* and *Guduchi Ghanavati* in *Vatarakta* (gout).

Clinical Contrive

Research Design: A Randomised Clinical study.

Ethical Aspect: An approval by the institution's ethics committee (DYPCARC/IEC/536/2022) of Dr. D.Y. Patil College of Ayurved and Research Centre, Pune-18 was obtained and thereafter matriculated with the India's clinical trial registry (CTRI/2023/03/050927). A comprehensive case record form was kept up to date, along with signed consent forms of all the study participants.

Source of Data: Patients attending OPD and admitted in IPD of the institute of Dr. D.Y. Patil College of Ayurved & Research Centre were recruited in the research.

Sample size and sampling technique: On the basis of prevalence, the sample size was determined: A total of 60 participants (i.e. 30 in each group) with dropouts taken into consideration were enrolled in the research study, using the computer-generated randomization method. The CONSORT chart of activities and patient's profile is provided in Figure 1.

Drug Source: *Guduchi* and *Kokilaksha* were procured and authenticated from FDA approved Ayurveda Pharmacy of Dr.D.Y.Patil College of Ayurved and Research Centre, Pimpri, Pune.

Table 1: Drug Description

Sr. No.	Group	Name of Drug	Botonical name	Family	Part used
1	Group A	*Guduchi*	*Tinospora cordifolia (willd.) Hook. f. & thoms.*	Menispermaceae	Stem
2	Group B	*Kokilaksha*	*Asteracantha longifolia Nees.*	Acanthaceae	*Panchanga*

Method of preparation

Ingredients: *Guduchi* stem: Water (1:4)

Guduchi coarse powder was obtained, added with four times of water and was heated until it is reduced to one fourth, transformed into *Ghana* as per the guidelines given in the sharangdhar samhita. Binding agentes were added to the mixture *(Ghana)*, and it was thereafter kept in hot oven to dry. Obtained granules were processed in a tablet pressing machine to yeild 250 mg tablet. Similary *Kokilaksha Ghanavati* was prepared.

Table 2: Analytical report

Tests	*Guduchi Ghanavati*	*Kokilaksha Ghanavati*
Description	Biconvex soft tablets	Biconvex hard tablets
Colour	Light dirty brown	Light black
Odour	Characteristic	Faint
Taste	Bitter	Bitter
Average weight	250 mg	250 mg
Diameter	8.33 mm	8.2 mm
Thickness	5.5 mm	5.5 mm
Hardness	5.0 kg/cm^2	3.0 kg/cm^2
Disintigration test	10 min: 02 sec	4 min
pH	6.2	6.0
Moisture content	4.6%	4.5%
ASH	3.11%	9.75%
AIA	1.14%	2.01%
Water soluble extractive	29.45%	19.45%
Alcohol soluble extractive	8.11%	6.44%

Implementation:

The patients were reviewed as per the criteria of inclusion and exclusion.

Inclusion criteria for the study were participants between the age of 18-70 years, who exhibited the clinical features of *vatarakta,* that include joint pain, swelling, tenderness, stiffness, burning sensation, or local colour changes in the skin, with serum uric acid within the range of 2.5-12 mg/dl.

Exclusion criteria for the study were individuals with severe systemic conditions, including renal disease, cardiac disease, or cerebrovascular disease, or those with secondary hyperuricemia associated with polycythaemia, leukaemia, or lymphoma. Injury that needs surgical intervention. Pregnant women or lactating mothers or any condition that impedes the treatment course was also excluded from the research study.

Table 3: Intervention

Group	Drug	Dose	Route of Administration	Time of Administration	*Anupana*
A	*Kokilaksha Ghanavati*	250 mg × 2	Orally	Morning - Evening (Before Meal)	Lukewarm water
B	*Guduchi Ghanavati*	250 mg × 2	Orally	Morning - Evening (Before Meal)	Lukewarm water

https://doi.org/10.47552/ijam.v16i1.5456 ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 16 (1), 2025; 136-141

Duration of the Trial: 14 days study, with follow-up on 7th and 14th day.

Table 4: Criteria for the evaluation and the scoring pattern

Symptoms	0	1	2	3
Sandhi shoola **(joint pain)**	No pain	Occasional tolerable pain	Frequent/ moderate pain	Persistent/ intense pain that disturbs sleep/ agony with each movement
Sandhi shotha **(joint swelling)**	Swelling not present	Not obvious swelling	Noticeable in < 2 joints	Visible in > 2 joints
Sankochan **(stiffness)**	Normal Movement	Mild difficulty	Moderate difficulty	Inability to move
Sparsha-asahatva **(tenderness)**	Absence of tenderness	Deep touch causes mild tenderness	Moderate level of tenderness from little touch.	Slightest touch results in extreme tenderness
Daha **(burning sensation)**	Absent	Transitory, lasting for a short period	frequent, self-aversion	Constantly, seek medical guidance
Local changes in the skin colour	No change	Mild	Moderate	Severe

Objective Criteria

- **Serum uric acid** (prior to and after intervention)
- **Visual analog scale**

Statistical Methods: SPSS software version 26 IBM was implemented to do statistical data analysis. The Mann-Whitney's test was used to evaluate distinction between the two groups' observations on an ordinal scale, while the Unpaired t test was employed for quantative observations. The Friedman test was used for ordinary scale data, and the Paired t test was adopted for quantitative observations within group analysis. At p value < 0.05, all tests were attained to be statistically significant.

Observations

Figure 1: CONSORT flow chart of activities and patient's profile throughout the research

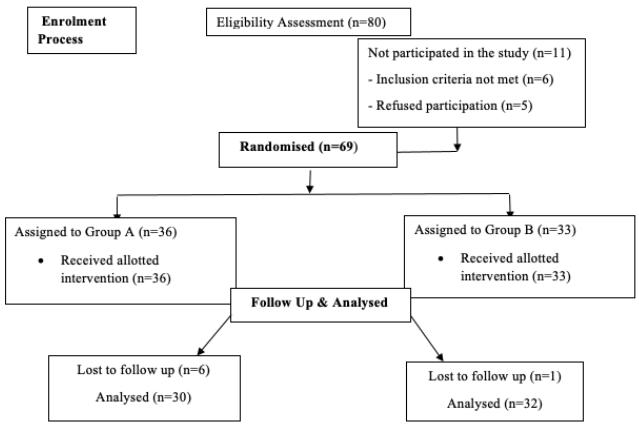

Table 5: Comparison of effect of intervention within groups before treatment (BT) and after treatment (AT). Descriptive statistics expressed in mean and standard deviation

Parameter	Group	Mean ± Standard Deviation		P value
		BT	AT	
Sandhi Shoola **(Joint Pain)**	Group A	1.9333 ± 0.58329	0.8333 ± 0.46113	< 0.05
	Group B	2.0313 ± 0.53788	0.3750 ± 0.49187	< 0.05
Sandhi Shotha **(Joint Swelling)**	Group A	0.9667 ± 0.55605	0.1333 ± 0.34575	< 0.05
	Group B	0.8125 ± 0.59229	0.4688 ± 0.56707	< 0.05
Sankochan **(Stiffness)**	Group A	0.9667 ± 0.31984	0.7000 ± 0.46609	< 0.05
	Group B	1.0625 ± 0.43533	0.1563 ± 0.36890	< 0.05
Sparsha-asahatva **(Tenderness)**	Group A	0.9333 ± 0.58329	0.3333 ± 0.54667	< 0.05
	Group B	1.2188 ± 0.65915	0.3750 ± 0.49187	< 0.05
Daha **(Burning Sensation)**	Group A	1.2000 ± 0.80516	0.3667 ±0.49013	< 0.05
	Group B	1.0625 ± 0.80071	0.3125 ± 0.47093	< 0.05
Local colour changes in the skin	Group A	0.1000 ± 0.30513	0.0667 ± 0.25371	> 0.05
	Group B	0.1250 ± 0.33601	0.000 ± 0.00000	< 0.05
VAS score	Group A	5.2000 ± 1.62735	1.6667 ±1.18419	< 0.05
	Group B	5.5000 ± 1.36783	0.6563 ± 0.93703	< 0.05
Sr. uric acid	Group A	6.2633 ± 1.88871	5.9300 ± 1.76560	< 0.05
	Group B	6.5609 ± 2.00896	6.0156 ± 1.84165	< 0.05

Table 6: Comparison between groups from day 0 to day 14. Expresed in mean rank and percentage effect

Parameter	Group	Mean Rank	Percentage effect (%)	P value
Sandhi Shoola **(Joint Pain)**	Group A	24.20	56.90	< 0.05
	Group B	38.34	81.54	
Sandhi Shotha **(Joint Swelling)**	Group A	38.63	86.21	< 0.05
	Group B	24.81	42.31	
Sankochan **(Stiffness)**	Group A	21.27	27.59	< 0.05
	Group B	41.09	85.29	
Sparsha-asahatva **(Tenderness)**	Group A	27.60	64.29	< 0.05
	Group B	35.16	69.23	
Daha **(Burning Sensation)**	Group A	32.68	69.44	> 0.05
	Group B	30.39	70.59	
VAS score	Group A	23.32	67.95	< 0.05
	Group B	39.17	88.07	

Table 7a and 7b: Comparison of effect of drug on serum uric acid level (between the group).

Table 7a

Group Statistics						
	Group	N	Mean	Stadard Deviation	Standard Error	Perentage
Serum uric acid	Group-A	30	0.3333	0.71406	0.13037	5.32
	Group-B	30	0.5453	0.59505	0.10519	8.31

Table 7b

Independent Samples Test									
Serum uric acid	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Significance level	t	df	Sig. (2-tailed)	Mean Diff.	Std. Error Difference	95% Confidence Interval of the Diff.	
								Lower	Upper
Equal variances	0.016	0.900	-1.273	60	0.208	-0.21198	0.16653	-0.54508	0.12113
Equal variances not			-1.265	56.607	0.211	-0.21198	0.16653	-0.54747	0.12352

Table 8: Number of patients with overall percentage effect

Sr. No.	Criteria of Assessment	Grade of Improvement	Number of Patients	
			Group A	Group B
1	75 - 100 %	Marked	6	20
2	50 - 74 %	Moderate	19	11
3	25 - 49 %	Mild	5	1
4	0 - 24 %	Poor	0	0

There was marked improvement seen in about 26 patients in the whole course of the treatment, 6 from Group A and 20 from Group B. Group A's 19 patients and Group B's 11 patients had moderate effect. 1 patient from B Group and 5 patients from A Group had mild improvement.

Demographic Data

Most subjects were from the age range of 31-40 years (29.03 %), 21-30 years (25.81%), 41-50 years (22.58%), reflecting disease prevalence trend in middle age, while young adults (21-30 years) were also affected, probably due to unhealthy eating practices, overtraining and disturbed sleep pattern. Homemakers comprised the highest occupational category impacted (32.26%), most likely as a result of sedentary life and exposure to cold water while carrying out household tasks, which triggers the *Vata*. 12.90 % of drivers suffered, possibly as an outcome of their profession's needs, requiring of repetitive tasks including shifting gear frequently, using of break and clutch, putting in long hours, unhealthy dietary pattern and disturbed sleeping schedule. Diet was a major factor, with 61.29 % having a mixed diet given that meat-rich diet is high in purine content.

Results

Sandhi shoola (joint pain), showed mean reduction from 1.9333 to 0.8333 and 2.0313 to 0.3750 in Group A and Group B, respectively, with B Group attaining better result (81.54%). For *sandhi shotha* (joint swelling), in Group A, mean declined from 0.9667 to 0.1333, while in B Group from 0.8125 to 0.4688, with Group A yielding 86.21 % improvement. *Sankochan* (stiffness) mean declined from 0.9667 to 0.7000 in Group A and in Group B (1.0625-0.1563), where Group B achieved 85.29 % improvement. In Group A, the mean for *sparsha-asahtava* (tenderness) decreased to 0.3333, and in Group B, it improved by 69.23 percent (1.2188-0.3750). Local colour changes in the skin: Group A showed a mean decrease from 0.1000 to 0.6667, with no statistical significance ($P>0.05$), while Group B improved from 0.1250 to 0.000 ($P<0.05$). Parameters on *daha* (burning sensation) and serum uric acid, both groups showed significant improvement (*daha:* 69.44% in A Group, with 70.59% in B Group, and serum uric acid: 5.32% in Group A and 8.31% in B Group), with no statistically significant variation on comparison ($P>0.05$). In Group A and Group B, mean score for visual analog scale lowered from 5.2000 and 5.5000 to 1.6667 & 0.6563, respectively. Group B reported higher relief percentage (88.07%).

Discussion

The *samprapti* (etiopathogenesis) of *vatarakta* begins with the vitiation of *vata* as well as *rakta*. Furthermore, the vitiated *rakta* occludes the course of the *vata*. And thereby, the type of *srotodushti* (vitiation of channels) seen is *sanga* (obstruction). The drug intervened was able to pacify *vata* resulting in reducing *Shoola* and *Shotha* without vitiating *rakta* and executing as *rakta prasadaka*.

***Guduchi* (*Tinospora cordifolia*):** In classical texts, *Guduchi* has been termed as *agrya dravya* for *vatarakta*. **(7)** Probable mode of action is by virtue of its characteristic trait, i.e. *rasa (tikta* (bitter), *katu* (pungent), *kashaya* (astringent)), *veerya (ushna), vipaka (madhura),* and *guna (guru* (heaviness), *snigdha* (unctuous)*).* **(8,9)** Its *vata-shaman* effect is due to *madhura vipaka, ushna veerya, guru* (heaviness) and

snigdha (unctuous) properties, which are precisely the contrary to the *vata dosha*. *Guduchi's tikta rasa* serves as *pitta shamak* and pacifies the vitiated *rakta* as well, following the *Ashraya-Ashrayi bhava* of *rakta* and *pitta*. **(10)** As *srotorodha* was eliminated and the *dosha* that led to the disease subsided, the core symptoms of the condition- *sandhi shoola* (joint pain), *shotha* (swelling), *daha* (burning sensation), *sparsha-asahatva* (tenderness) and stiffness-were reduced. Likewise, the drug's *rasa* and *veerya* also facilitate *agni dipana* (stimulates digestive fire), *aam-pachana* and its *tridosha shamak* action (balancing all three *doshas*). *Guduchi's rasayana* quality helps to strengthen the immune system, prevent disease recurrence and relapse, and supports the development of optimal qualities of *dhatu* (bodily tissues). By promoting vitality and resilience, *rasayana* contributes to overall health and well-being. **(11)** Scientific studies on *guduchi* has shown the positive findings due to its variety of chemical constituents found, including alkaloids, sesquiterpenoid, phenolics, diterpenoid lactones like tinosporin etc. Demonstrated its anti-arthritic, anti-inflammatory, immuno-modulatory, along with slight analgesic effect. Its strong anti-inflammatory property is comparable to indomethacin in terms of effect, and its mechanism of action seemed to be analogous to that of NSAIDs. **(12,13)** As a result, it reduces pain, stiffness and swelling, all of which are secondary to inflammation.

***Kokilaksha* (*Asteracantha longifolia*):** The principal *doshas* implicated in the disease's etiopathogenesis are *vata* and *pitta*. *Kokilaksha's madhura rasa, guru* and *snigdha guna*, alleviates the vitiated *vata* and due to its *tikta rasa*, it pacifies the *pitta*, which also calms the vitiated *rakta*. **(14,15)** The drug's *vata-pitta hara* characteristic benefits to ease pain, stiffness, and burning sensation. With its *shotha-hara* action, it lowers swelling. Research has identified polyphenolic compounds named B-sitosterol and phytoconstituent lupeol in *kokilaksha*. Contributing to its anti-inflammatory and anti-arthritic effects respectively. **(16,17)**

Conclusion

The results of both the intervened drugs showed statistically significant improvement ($P<0.05$), addressing all study parameters. *Kokilaksha Ghanavati* exhibited better effectiveness on parameter, ie. *shotha* (swelling). While *Guduchi Ghanavati* excelled on other parameters like *sandhi shoola* (joint pain), *sankochan* (stiffness), VAS score and local color changes in the skin. Overall, *Guduchi Ghanavati* was more effective, but *Kokilaksha Ghanavati* showed major improvement in one of the primary symptoms of the disease (*shotha*-86.21%), along with visible improvement in other parameters as well. The positive impact of it on *vatarakta* is also undeniable, highlighting its potential for *vatarakta* management.

Study Limitation

The duration of the research and sample size were the limitations to draw concrete conclusions.

Source(s) of funding: None

Conflict of interest: None

References

1. Boloor A, Nayak R. Exam Preparatory Manual for Undergraduates. 3rd ed. Jaypee Brothers Medical Publishers; 2021. 724-26.
2. https://www.ncbi.nlm.nih.gov/books/NBK546606/ dated 14-07-2024 time 15:01 IST
3. Shastri K V. Susruta samhita of maharsi. Volume I, chikitsa sthana, chapter 5th. Varanasi; Chaukhambha publication; 2016(reprint). 37-41p.
4. Sastri K, Chaturvedi G. The charak Samhita of agnivesa, Volume II, Chikitsa sthana, vatashonitha chikitsa adhyaya, chapter 29, verse 5-9. Varanasi; Chaukhambha bharati academy; 2018(reprint). 820p.
5. Sastri K, Chaturvedi G. The charak Samhita of agnivesa, Volume II, Chikitsa sthana, vatashonitha chikitsa adhyaya, chapter 29, verse 10-11. Varanasi; Chaukhambha bharati academy; 2018(reprint). 820p.
6. Bhavana KM, Umesh C, Sajjanar N, & Gopala KG. A Randomized Comparative Clinical Study to evaluate the effect of Bodhi Vruksha Twak Kashaya with Madhu and Guduchi Kashaya in the Management of Vatarakta with special reference to Gouty Arthritis. J Ayurveda Integr Med Sci. 2020; 5(02): 22-29. https://doi.org/10.21760/jaims.v5i02.859.
7. Gupta K.A. Astangahrdayam of Vagbhata, uttar sthana, vajikarana vidhi adhyaya, chapter 40, verse 50. Varanasi; Chaukhambha prakashan; 2019 (reprint). 832p.
8. Bhavamishra. Bhavapraksha Nighantu, Guduchyadi varga, verse 8-10, Varanasi; Chaukhambha bharti academy; 2015. 257-59p.
9. Sharma P V. Dravyaguna vijnana, vegetable drugs, Vol II. Varanasi; Chaukhambha Bharati Academy; 2020(reprint). 762p.
10. Gupta K.A. Astangahrdayam of Vagbhata, uttar sthana, vajikarana vidhi adhyaya, chapter 11, verse 26. Varanasi; Chaukhambha prakashan; 2019 (reprint). 117p.
11. Sastri K, Chaturvedi G. The charak Samhita of agnivesa, Volume II, Chikitsa sthana, rasayana adhyaya, chapter 1st, verse 7-8. Varanasi; Chaukhambha bharati academy; 2018(reprint). 820p.
12. Upadhyay Ak, Kumar K, Kumar A, Mishra HS. Tinospora cordifolia (Willd.) Hook. f. and Thoms. (Guduchi) – validation of the Ayurvedic pharmacology through experimental and clinical studies. Int J Ayurveda Res. 2010;1(2): 112-121. https://doi.org/10.4103/0974-7788.64405

13. Joshi G, Kaur R. Tinospora Cordifolia: A Phytopharmacological Review. Int J Pharm Sci Res. 2016;7(3): 890-97.
14. Bhavamishra. Bhavapraksha Nighantu, Guduchyadi varga, verse 224-225, Varanasi; Chaukhambha bharti academy; 2015. 402p.
15. Sharma P V. Dravyaguna vijnana, vegetable drugs, Vol II. Varanasi; Chaukhambha Bharati Academy; reprint 2020. 566p.
16. Samrit S R, Kamble N, Dambhare A, Hemke A, Umekar M. Preliminary phytochemical screening of ethanolic extract of Astercantha longifolia (Hygrophylla schulli) roots along with various activities. World journal of pharmaceutical research. 2020; 9(15):1267-79.
17. Patra A, Jha S, Murthy PN. Phytochemical and Pharmacological Potential of Hygrophila spinosa T. Anders. Phcog Rev. 2009;3(6):330-41.

*****