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Research Article

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Safety and Efficacy of *Charakokta Raktapachak Yoga* in Patients of Urticaria (Kotha) Caused Due to Dooshivisha – A Randomized Controlled Trial"

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Abstract: This controlled clinical study aimed to assess the safety and efficacy of Charkokta Raktapachak Yoga in treating Dooshivishajanya Kotha (urticaria), a condition known for its challenging recurrence. Two groups, each comprising 30 patients, were formed: a standard group receiving Tab. Cetrizine 10mg OD, and an experimental group receiving Tab. Raktapchak Yoga 500mg/day in two divided doses for 42 days. Follow-ups occurred every 7 days. The study evaluated manifestations such as raised edematous swelling (kotha), itching (kandu), burning sensation (daha), and pricking sensation (toda). Objective parameters like Hb, ESR, AEC, and stool examination were assessed before and after the study. Statistical analysis revealed significant inter-group differences after treatment for urticaria ($p = 0.0047$), itching ($p < 0.0001$), pricking sensation ($p = 0.0025$), and burning sensation ($p = 0.0018$). In the experimental group, significant improvements were observed in objective parameters: hemoglobin levels ($p = 0.0026$), ESR ($p < 0.0001$), AEC levels ($p < 0.0001$), and stool examination ($p = 0.0176$). Symptoms such as the urticarial wheel, itching, pricking, and burning sensation were alleviated more in the experimental group than in the control group. Recurrence of symptoms was reduced in the experimental group post-treatment compared to the standard group. Objective parameters improved in the experimental group, affirms the safety and efficacy of Charkokta Raktapachak Yoga in treating urticaria caused by Dooshivisha.

Keywords: Dooshivisha, Kotha, Urticaria, Raktapachak Yoga, kandu, daha, toda

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1. INTRODUCTION

The substance that causes sadness (vishanna) in the world (jagad) is called Visha. There are two types of Vishayoni– Plant origin (Sthavara) and Animal origin (Jangama).[1] A poison, either plant origin, animal origin or artificial, when not removed from the body completely and becomes weak by anti-poisonous remedies, fire(*davagni*), wind(*vata*), the sun (*atapa*), or this less potent poison is called as *Dooshivisha*. It does not cause any mortality but resides in the body for many years. [2] It causes cumulative toxicity effects on the body. Bhavprakash classified artificial poisons in Garavisha and Dooshivisha.[3] Aggravating factors such as *Place (Desha), season (Kala), food (Anna) and* sleep during day time (*divanidra*) caused vitiation of body fundaments by Dooshivisha .[4] Bioaccumulation of toxins shows similarity to the concept of Dooshivisha. When absorption of toxic substances is faster than its catabolism and excretion in the body, it causes bioaccumulation of that poison and leads to chronic poisoning.[5] Acharya Charkacharya explained Kotha (urticaria) is one of the symptoms of Doshisha. Dooshivisha causes vitiation of the fundamentals of the body (tridoshas with dhatu). The vitiated blood (rakta dhatu) causes Psoriasis (kitibha), urticaria (kotha), etc.[6] Acharya Sushruta also explained urticaria (Koth) as one of the symptoms of Dooshivisha.[7] Madhavkara in Madhavnidan explains the etiopathology of kotha.[8]. When the body comes in contact with incompatible food and material, it causes the symptom urticaria. E.g. Particular food, material, *cold wind*, etc. Kotha (urticaria) has raised edematous swelling, itching, pricking, and burning sensations as manifestations. The appearance of this kotha is very similar to urticaria. Urticaria is an allergic reaction and is chronic. Urticaria is raised edematous wheals in the dermis. Release of histamine, prostaglandin D2, bradykinin, and leukotriene C4 from mast cells and basophils causes urticaria lesion due to extravasation of fluid into the dermis.[9] Urticaria may not be life threatening, but its severe form cause disturbances in daily routine life as it chronic in nature.[10] Treatment of Dooshivisha is fomentation of the body& cleansing by emetics & purgative medicated drugs. Then followed by Dooshivishari Antidot (agad) daily.[11] In kotha caused by doshivisha, impurity of blood is more, so normalcy of blood (rakta dhatu) in treatment need to be done. Charkacharya mentioned that blood-letting (*Siravedha*) is also an effective treatment for *Dooshivisha*. [12] Fever treatment chapter (*Jwara Chikitsa*) of Charaka Samhita, given *Vishamajwara* etiopathoenisis, is similar to *Dooshivisha*'s. So, the mentioned *Dhatu Panchak Yoga* can be used in conditions with the same etiopathogenesis[13]. The use of raktapachak yoga can prove effective in the treatment of urticaria(kotha) caused by dooshivisha, where the impurity of blood is extensive. This study aims to assess the efficacy and safety of *Charakokta Raktapachaka Yoga* in treating *kotha caused by Dooshivisha* with special reference to urticaria. This study's objectives are compiling relevant literature, authentication, preparation, and standardization of raktapachak yoga, and assessing the efficacy &safety of *charakokta raktapachaka yoga* in urticaria caused by dooshivisha.

2. MATERIALS AND METHODS

Table 1: Ingredients of Raktapachak Yoga

Sr. No.	Ingredient	English Name	Latin Name	Part Used in the formulation
1	*Patola*	Pointed Gourd	*Trichosanthes dioica*	Fruit
2	*Sariva*	Indian Sarsaparilla	*Hemidesmus indicus*	Root
3	*Musta*	Nut Grass	*Cyperus rotundus*	Dried rhizome
4	*Patha*	Velvet leaf	*Cissampelos pareira*	Root
5	*Katuki*	Hellebore	*Picrorhiza kurroa*	Dried rhizome with Root

Table 1 explains all the ingredients of raktapachak yoga, their English name, Latin name, and the part used for medicinal preparation.

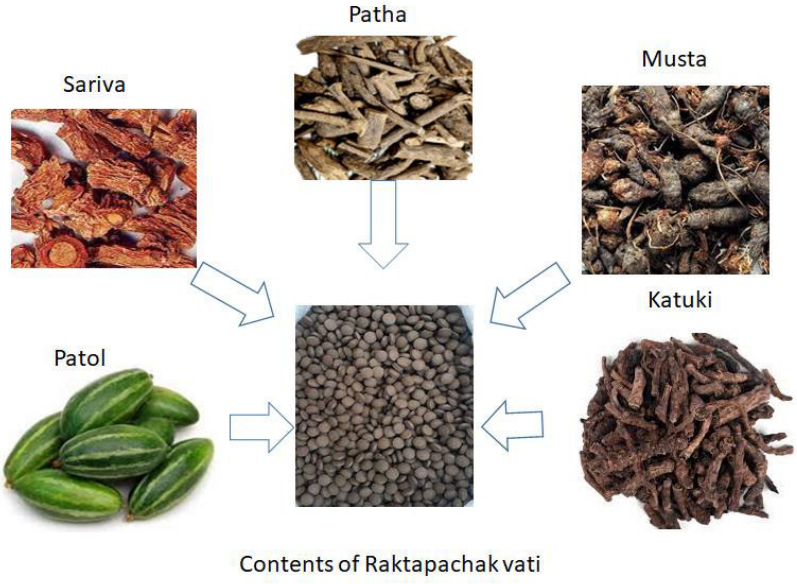


Fig 1: Contents of raktapachak yoga

Taste (rasa), post-digestive effect *(Vipak)*, Potent energy (*Veerya)*, *properties(guna)*, and action on *fundamentals of the body* for each ingredient of raktapachak yoga according to *Dravya Guna Vigyana* are described.[14] The groups (*Gana)* from Charaka Samhita[15] and Sushruta Samhita[16] have listed below-

1) Patol (*Trichosanthes dioica)* – Bitter, pungent-pungent- Hot (Tikta,katu-Katu-ushna), Light, Dry (Laghu, ruksha) Balances pitta and kapha (Pitta-kapha shaman),

Gana- Patoladi, Aragvadhadi, Truptighna(relieve the feeling of food satisfaction), Trushna Nigrahana(relieve excessive thirst)

2) Sariva (*Hemidesmus indicus*) – sweet- sweet- coolant (Madhur-Madhur- sheet), Heavy, oily (Guru, Snigdha). Balances all three doshas (Tridoshashaman, Pittashaman, especially),

Gana- Stanya Shodhana (cleanse and detoxify breast milk), Jwarahara(treating fever), Daha Prashamana (relieving burning sensation), Purisha Sangrahaniya (improve bulk of feces), Madhura Skandha(sweet-tasting group of herbs),

3) Musta (*Cyperus rotundus*) - Bitter, Pungent, astringent –pungent- cold (Tikta, Katu, Kashaya-katu-sheeta) Light. Dry (Laghu, ruksha), Balances Kapha-pitta (kapha-pitta shamak),

Gana-Lekhaniya (useful in obesity treatment), Trushnanigrahana (thirst satiating), Kandughna (relieving itching), Stanyashodhana (cleans and detoxifying breast milk), Mustadi,Vachadi

4) Patha (*Cissampelos pareira)* - bitter, pungent-pungent-hot (Tikta, Katu- katu-ushna), Light, piercing (Laghu, Tikshna) Balances three doshas (Tridoshashaman)

Gana- Sandhaniya(healing wound and fracture), Jwarahara (useful in treatment of fever) , Stanyashodhana(cleans and detoxify breast milk), Mustadi, Aragvadhadi, Pippalyadi, Ambashthadi, Bruhatyadi, Patoladi

5) Katuki (*Picrorhiza kurroa)* - bitter, pungent- pungent-hot (Tikta, Katu- katu- Ushna) Light (Laghu), balances pitta (Pittashamak),

Gana- Bhedaniya (piercing), Lekhaniya (useful in obesity treatment, stanyashodhana (cleans and detoxifies breast milk), Tikta Skandha (bitter tasting group of herbs), Patoladi, Pippalyadi snd Mustad

2.1. Botanical Constituents of contents of Raktapachak Yoga[17]

1) Patola *(Trichosanthes dioica)* – Colocynthin, trichosanthin, saponin, hentriacontane, trichosanthin, saponin
2) Sariva*(Hemidesmus indicus)* - Essential oil, saponin, resin, tannins, sterols and glucosides
3) Musta*(Cyperus rotundus)* – cyperene, humulin, zierone, selinene,copaene, limonene
4) Patha*(Cissampelos pareira)*- Alkaloids, saponin and quaternary ammonium bases, flavanol andSterol
5) Katuki*(Picrorhiza kurroa)*- Glucoside (Picrorhizin), pikuroside, androsin, cucurbitacin glycosides

2.2. Reported Pharmacological properties of contents of Raktapachak Yoga:

- Patola *(Trichosanthes dioica)* –Chemo Preventive[18], Laxative[19], Nematocidal and Anthelmintic[20], Anti-inflammatory & anti nociceptive[21], Anti-hyperglycaemic & antihyperlipidemic[22]
- Sariva *(Hemidesmus indicus)* - Anti-microbial[23]
- Musta*(Cyperus rotundus)* - Anti-Inflammatory[24] , Anti-Pyretic[25], Analgesic, Tranquillizing[26], Anti-convulsion[27]
- Patha*(Cissampelos pareira*)- Antinociceptive and anti-arthritic[28], Anti-inflammatory[29], Anti-fertility[30], Antioxidant[31], Anti-haemorrhagic[32]
- Katuki*(Picrorhiza kurroa)*- Hepatoprotective[33], Anti-Asthmatic[34], Anticancer[35], Anti-Microbial[36], Immunomodulator[37]

2.3. Authentication and standardization of ingredients of Raktapachak Yoga[38]

All five ingredients for Raktapachak yoga viz patol*(Trichosanthes dioica)*, sariva*(Hemidesmus indicus)*, musta*(Cyperus rotundus)*, katuki*(Picrorhiza kurroa)* and patha*(Cissampelos pareira*) were collected from local authentic market, vashi, navi Mumbai. They were identified, authenticated, and standardized at the Quality control laboratory of Alarsin Pharmaceuticals Andheri Mumbai. All the herbal ingredients passed the quality parameters described in the API.

2.4. Preparation and standardization of Raktapachak Yoga

Useful parts of ingredients of raktpachak yoga such as Patol*(Trichosanthes dioica)*leaves, Kutki *Picrorhiza kurroa)*stembark, Sariva*(Hemidesmus indicus)*roots, Patha*(Cissampelos pareira*) roots, Musta*(Cyperus rotundus)*Rhizomes and were dried well. Each drug was mixed in equal quantities of 400gm for a batch size of 2 kg using mass pulveriser and with the help of Sieve no.80, it transferred in a mass shifter. This powder was mixed in a mass mixture. A decoction made by the above ingredients were mixed with prepared fine powder. The obtained powder and decoction mixture was triturated in an end runner for 9 hours.[39] This mixture was dried by an electric dryer at a maximum of 600^0C. In dried mass, excipients were added like SMHB 4gm and SPHB 0.4 gm, MCC 160 gm, and Starch 240 gm. Then, granules were made by multimill with sieve no. 2. Tablets weighing 250 mg each were made using the tableting machine. 3 batches of similar tablets were prepared.
The scientific pharmaceutical analysis of *Raktapachak Vati* (Tablet) was done according to the required parameters at the quality control laboratory of Alarsin Pharmaceuticals, Andheri, Mumbai.

3. EXPERIMENTAL STUDY

3.1. Ethical statement

Institutional Ethics Committee (IEC) of the D. Y. Patil, Deemed to be the University School of Ayurveda, Nerul,

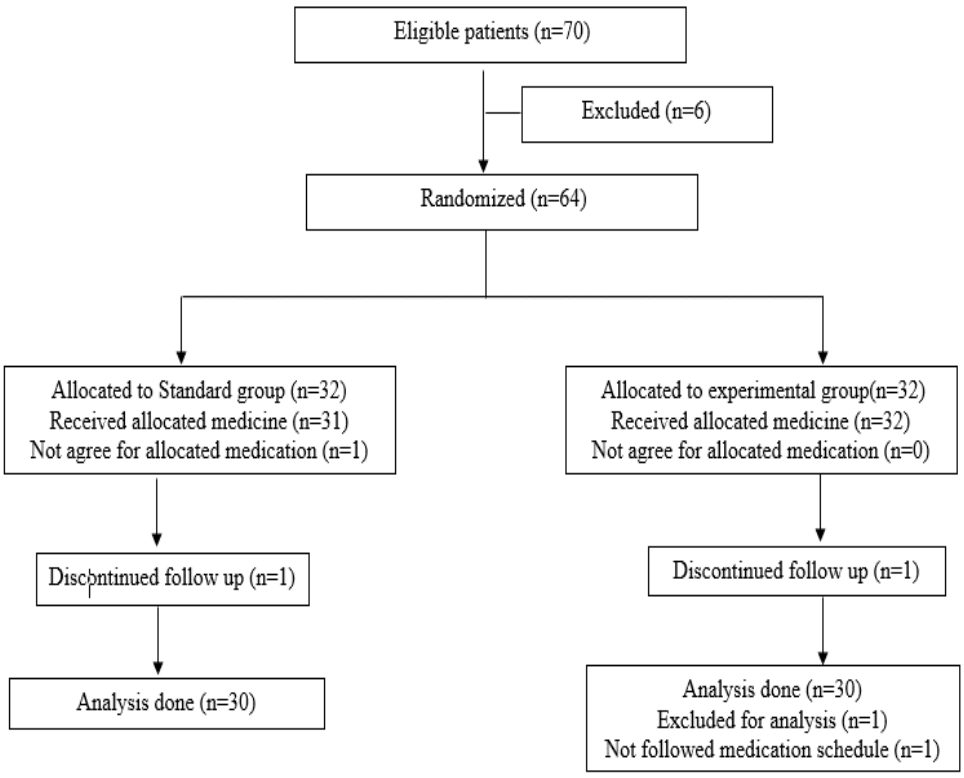
Navi Mumbai, approved the study, Ref no. DYPUSA/27-A(14/2/2022). CTRI registration was done CTRI Reg. No. CTRI/2022/03/041186 Ref No. REF/2022/3/052374 ,(17/03/2022). Informed consent was obtained from each patient before the study, and drug intervention and further publication were explained to them.

3.2. Inclusion criteria

1) Age of the patient- 18 to 60 years
2) Both male and female patients included
3) Patients of *Kotha (urticaria)caused by dooshivisha* show edematous wheel, itching, burning, and pricking sensation for one year.
4) Patients continuously exposed to incompatible food, chemicals, and pesticides at the workplace.

3.3. Exclusion criteria

1) Age not as per inclusion criteria
2) Patients with major systematic complications.
3) Patients taking steroid therapy for skin diseases and complicated injuries.
4) Females having pregnancy and breastfeeding mothers.
5) Patients not willing to receive treatment
6) Patients absent for follow-up
7) Any patient with a serious condition requiring emergency management should be withdrawn from the study and treated accordingly.



3.4. Randomization of patients

Randomization of the patients was done using a simple method, i.e., flipping a coin. Patients were distributed into two groups- the control group and the standard group. Randomization was done by the person not involved in clinical evaluation and intervention.

3.5. Clinical Study

A controlled clinical study was conducted to assess the efficacy and safety of charkokta *Raktapachaka Yoga* in *Dosshivishajanya Kotha*. A case record form was designed and Informed consent was obtained from every included patient.

Type of study: Interventional study.
Sample size: minimum 60 patients
Sampling Type: Purposive
Group Design: Parallel group design
1) Standard Group (Group A)- standard drug (30 Patients)
2) Experimental Group (Group B) – Experimental drug (30 Patients)
Standard Group (Group A) were given Tab. Cetrizine 10mg o.d/Day and Experimental Group (Group B) – Tab. were given Raktapachak Yoga 500mg/day in 2 divided doses with warm water as anupan. (Dose adjusted as per the weight of the patient) Tab. Cetrizine 10 mg sos. The period allotted for the study was 42 days, and follow-ups were taken after every 7 days. Investigations were routine laboratory investigations before and after clinical trials like CBC, absolute eosinophils count, ESR, and stool examination.

3.6. Parameters

3.6.1. Subjective parameters

Kotha (Raised oedematous wheels), Kandu (Itching), Toda (pricking sensation), Daha (Burning sensation). Gradations for each symptom- 0, 1, 2, 3 for none, mild, moderate, and severe.

Table-2 Urticaria activity score (USA) as per India Journal of Dermatology [40]		
Score	**Wheals/ 24 hrs**	**Pruritus**
0	None	None[40]
1	Mild (<20)	Mild present but not annoying or troublesome [40]
2	Moderate (20-50)	Troublesome but does not interfere with sleep [40]
3	Intense (>50 or large confluent area of wheals)	Severe pruritus which is sufficiently troublesome to interfere with normal daily activity or sleep [40]

3.6.2. Objective parameters[41]

1) CBC
2) Erythrocyte Sedimentation Rate (ESR)
3) Absolute Eosinophils count
4) Stool examination

3.7. Assessment of Safety

No adverse effect due to Raktapachak yoga was noted. It was assessed by Global assessment of Safety which are as follows,

Table 3 Evaluation of Tolerability (Safety) by Global assessment of Adverse effects[42]	
Occurrence of Adverse effects	**Tolerability Grade**
Excellent Tolerability: No event reported.	1
Good Tolerability: Mild adverse events which subsided with or without medication.	2
Fair Tolerability: Moderate to severe adverse events reported which subside with or without medications and do not necessitate stoppage of study medication	3
Poor Tolerability: Severe adverse events which necessitated stoppage of the study treatment.	4

3.8. Follow up

For assessment of subjective parameters, follow-up of the patients was done every 7 days up to 42 days, and data was collected before and after treatment. Laboratory investigations of blood like Hb, ESR, AEC, and stool examination were done before and after treatment to assess objective parameters.

3.9. Statistical analysis

Assessment of subjective parameters like raised edematous swelling (kotha), itching (kandu), burning sensation(daha), and picking sensation (toda). The intra-group comparison of before and after the study was done with the Wilcoxon matched-pairs signed-ranks test.[43] The Mann-Whitney Test was applied for inter-group comparison before and after the study for the standard group and experimental group.[44]

Assessment of objective parameters like Hb, ESR, AEC. A paired t-test was applied for an intra-group comparison of before and after treatment.[45] An unpaired t-test was used for inter-group comparison of before and after treatment i.e for the standard group and experimental group.[46]

Assessment of stool examination before and after treatment was done with Chi-square Test and degree of freedom 1. [47]

3.10. Enrolment of patients

70 volunteer patients were included in the study after screening from April 2022 to December 2022. Six patients were excluded from the study because they didn't want to give written informed consent. Then, 64 patients were distributed equally into the control and experimental groups after randomization. During the clinical trial, one patient was excluded from the control group as he did not agree to take medication. One volunteer participant from each group was excluded because they discontinued their follow-up. One participant from the experimental group was excluded before statistical analysis because of not following the medication schedule in the last two weeks of the trial. The final statistical analysis was done on 60 patients, 30 from each group who had completed the trial as per protocol.

3.11. Baseline characteristics

Statistical differences were not present in control group and experimental group including patients' age (included between 18-60 years), gender, religion, occupation, prakruti, agni, koshta, mansbhava, history of affected by any visha and incompatible food. Patients with severe co-morbidity, other skin diseases, burns, steroidal therapy, and conditions like pregnancy and lactation were excluded.

Table-4 Baseline Characteristics			
	Standard group n=30	**Experimental group n=30**	**Percentage**
Sex			
Male	18	14	53.33%
Female	12	16	46.64%
			P-value
Age (Mean+ SD)	38.57 ± 8.86	41.23 ± 8.68	0.2436

3.12. Data Presentation

Data presentation includes demographic details – age, gender, religion, occupation, prakruti, agni, koshta, mansbhava, affected by any visha and incompatible food. The final result was drawn based on improvement in symptoms of chronic urticaria and its objective parameters like Hb, ESR, AEC, and stool examination.

3.13. Demographic details

Demographic details of 60 patients are given below

- ***Age***

The age group 31 to 50 years (33.33%) was affected the most by kotha (urticaria). This vayavastha is madhyam and pitta predominance. Predominance pitta easily gets aggravated due to aggravating factors, and in combination with vitiated kapha-vata, it causes kotha.

- ***Sex***

Generally, middle-aged females are more affected by chronic urticaria than males. In the present study, out of 60 patients, 53.33% were male.

- ***Occupation***

People doing vigorous work (36.67%), farmers, and factory workers are affected more. People doing sedentary jobs (33.33%), like IT and call center jobs, were also affected more. In these jobs, shift duties, stress, and bad eating habits cause vitiation of vata, kapha, and pitta. Vitiated doshas ultimately cause raktaprodoshaj vikar like kotha.

- ***Marital status***

Out of 60 patients, 80% of people who are married belong to the middle age group and were found affected with kotha.

Agni: 30% of patients are found in the Vishamagni state. It causes agnimandya, which leads to the production of aam and tridoshaprakop. They play an important role in the pathogenesis of chronic urticaria.

Koshtha: Most patients have kosha (36.67%), which shows the dominance of pitta dosha.

Diet: In the diet-wise distribution of patients, 11.67% were shakahari, 51.67% were mishrahari, and 36.67% were taking aniyamit ahara. A mixed diet is incompatible, which causes skin diseases like kotha.

Prakruti: Pitta vata predominant prakruti patients (are affected more than patients with other prakruti. After this, Vata-kaphaj prakruti patients (33.34%) showed predominance in chronic urticaria. Pitta is the predominant dosha in kotha.

Manasbhava: Patients with rajas manas bhav i.e paitta predominance (65%) are prone to skin disease like kotha.

Histoty of vishaktata: 30% of patients with a jangam visha history and 70% of patients with a sthavar vish history have kotha. This poison remains in the body and causes skin disease symptoms whenever favorable conditions occur.

Virrudha-ahar: Mostly, all patients with kotha have a history of virudhha-ahar. Virrudha-ahar is one of the main causes for raktapradoshaj vikar like kotha.

Table 5- Demographic details

Sr. No	Characteristics	Percentage of the most affected group	
1	Age	33.33%	Age group 31 to 50 years
2	Sex	53.33%	Male
3	Occupation	36.67%	vigorous work
4	Marital status	80%	married who belong to middle age group
5	Agni	30%	vishamagni
6	Koshta	36.67%	mrudu koshtha
7	Diet	51.67% 36.67%	mishrahari, aniyamit ahara
8	Prakruti	41.66%	pitta-vata predominance
9	Manasbhava	65%	Rajas manas bhava
10	History of vishaktata	70% 30%	Shavarvisha history Jangamvisha history
11	Virrudhaahar	100%	Visrudhaahar history

4. RESULTS

The results are presented as follows:

Outcome assessment of Subjective Parameters:

1) Raised edematous swelling (Kotha)

Table 6 – Statistical analysis of raised edematous swelling (kotha)				
	Standard Group		Experimental Group	
Sample Size (n)	30	30	30	30
Mean ± SD	2.10 ± 0.80	01.57 ± 0.94	2.00 ± 0.74	0.90 ± 0.66
Mean (Range)	2 (1 – 3)	2 (0 – 3)	2 (1 – 3)	1 (0 – 2)
Intra-Group Comparison	Wilcoxon matched-pairs signed-ranks test		Wilcoxon matched-pairs signed-ranks test	
	The sum of all signed ranks (W) = 105.00 Number of pairs = 14		The sum of all signed ranks (W) = 378.00 Number of pairs = 27	
P value	0.0001, extremely significant.		0.0001, extremely significant.	
Inter-Group Comparison	Mann-Whitney Test			
	Mann-Whitney U-statistic = 259.50 U' = 640.50			
P value	The two-tailed P value is 0.0047, which is considered very significant.			

In Table 6, for the Standard Group, the median values of *Kotha* before and after treatment were 2 (1 – 3) and 2 (0 – 3), respectively, with significant differences (p = 0.0001) .In the Experimental Group, the median values of *Kotha* before and after treatment were 2 (1 – 3) and 1 (0 – 2), respectively, with statistically significant differences (p = 0.0001).The inter-group comparison showed a statistically significant difference between the two groups after treatment (p = 0.0047).

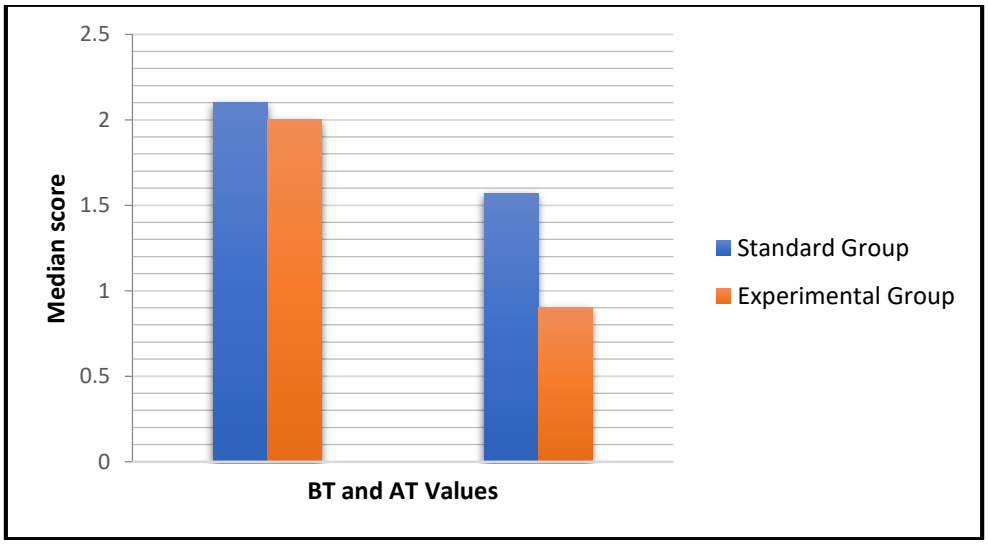


Fig. 3 Assessment of edematous swelling (kotha) in Two Groups

From Fig. 3, in the experimental group, patients received better relief in urticarial wheel symptoms after ingestion of raktapachak yoga. The recurrence rate was also decreased.

2) Itching (Kandu)

Table 7 Statistical analysis of itching (kandu)				
	Group A		Group B	
Sample Size (n)	30	30	30	30
Mean ± SD	2.07 ± 0.78	1.63 ± 0.72	1.93 ± 0.74	0.60 ± 0.56
Mean (Range)	2 (1 – 3)	2 (0 – 3)	2 (1 – 3)	1 (0 – 2)
Intra-Group Comparison	Wilcoxon matched-pairs signed-ranks test		Wilcoxon matched-pairs signed-ranks test	
	Sum of all signed ranks (W) = 91.00 Number of pairs = 13		Sum of all signed ranks (W) = 406.00 Number of pairs = 28	
P value	0.0001, extremely significant.		0.0001, extremely significant.	
Inter-Group Comparison	Mann-Whitney Test			
	Mann-Whitney U-statistic = 138.50 U' = 761.50			
P value	The two-tailed P value is < 0.0001, considered extremely significant.			

In Table 7, for the Standard Group, the median values of *Kandu* before and after treatment were 2 (1 – 3) and 2 (0 – 3), respectively, with statistically significant differences (p = 0.0001).In the Experimental Group, the median values of *Kandu* before and after treatment were 2 (1 – 3) and 1 (0 – 2), respectively, with statistically significant differences (p = 0.0001).The inter-group comparison showed a statistically significant difference between the two groups after treatment (p < 0.0001).

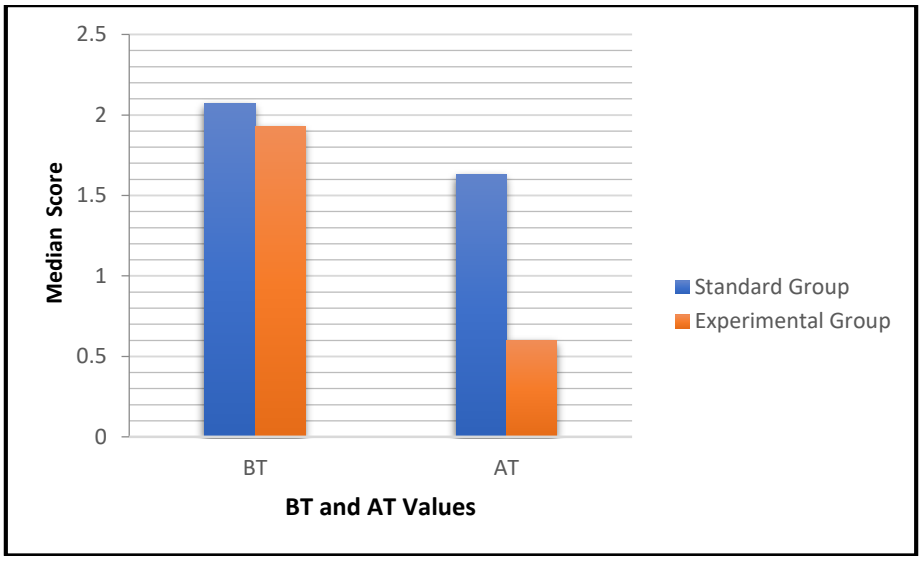


Fig.4 Assessment of pruritus (Kandu) in Two Groups

In Fig.4, patients in the experimental group received better relief from pruritus after taking raktapachak yoga medication.

3) Pricking sensation (Toda)

Table 8: Statistical analysis of Pricking sensation (Toda)

	Group A		Group B	
Sample Size (n)	30	30	30	30
Mean ± SD	1.80 ± 0.81	1.47 ± 0.78	1.97 ± 0.67	0.80 ± 0.71
Mean (Range)	2 (0 – 3)	2 (0 – 3)	2 (1 – 3)	1 (0 – 2)
Intra-Group Comparison	Wilcoxon matched-pairs signed-ranks test		Wilcoxon matched-pairs signed-ranks test	
	Sum of all signed ranks (W) = 55.00 Number of pairs = 10		Sum of all signed ranks (W) = 378.00 Number of pairs = 27	
P value	0.0020, considered very significant		0.0001, extremely significant.	
Inter-Group Comparison	Mann-Whitney Test			
	Mann-Whitney U-statistic = 246.00 U' = 654.00			
P value	The two-tailed P value is 0.0025, which is considered very significant.			

In Table 8, for the standard group, the median values of *Toda* before and after treatment were 2 (0 – 3) and 2 (0 – 3), respectively, with statistically significant differences (p = 0.0020).In the Experimental Group, the median values of *Toda* before and after treatment were 2 (1 – 3) and 1 (0 – 2), respectively, with statistically significant differences (p = 0.0001).The inter-group comparison showed a statistically significant difference between the two groups after treatment (p = 0.0025).

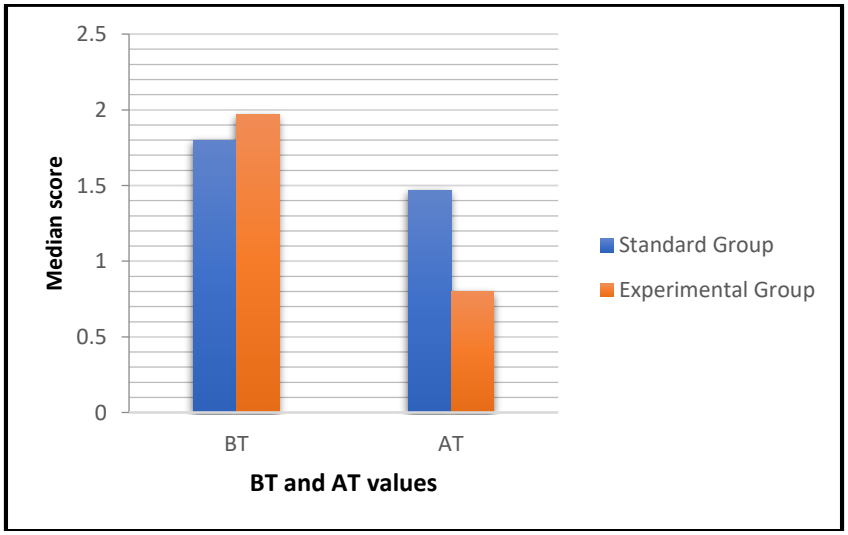


Fig.5 Assessment of pricking sensation (Toda) in Two Groups

Fig.5 As shown in the chart, a symptom of the pricking sensation was not relieved significantly in the control group after medication. In the experimental group, patients got relief from symptom pricking sensation significantly and relapsed much less.

4) Burning sensation (Daha)

Table 9 Statistical analysis of burning sensation (Daha)				
	Group A		Group B	
Sample Size (n)	30	30	30	30
Mean ± SD	1.43 ± 0.73	1.03 ± 0.81	1.50 ± 0.57	0.37 ± 0.49
Mean (Range)	1.5 (0 – 3)	1 (0 – 3)	2 (0 – 2)	0 (0 – 1)
Intra-Group Comparison	Wilcoxon matched-pairs signed-ranks test		Wilcoxon matched-pairs signed-ranks test	
	The sum of all signed ranks (W) = 78.00 Number of pairs = 12		The sum of all signed ranks (W) = 406.00 Number of pairs = 28	
P value	0.0005, extremely significant		< 0.0001, extremely significant.	
Inter-Group Comparison	Mann-Whitney Test			
	Mann-Whitney U-statistic = 246.00 U' = 654.00			
P value	The two-tailed P value is 0.0018, which is considered very significant.			

In table-9, the following details are given for the standard group, the median value of *Daha* before and after treatment was 1.5 (0 – 3) and 1 (0 – 3), respectively, with statistically significant differences (p = 0.0005).In the Experimental Group, the median values of *Daha* before and after treatment were 2 (0 – 2) and 0 (0 – 1), respectively, with statistically significant differences (p < 0.0001). The inter-group comparison showed a statistically significant difference between the two groups after treatment (p = 0.0018).

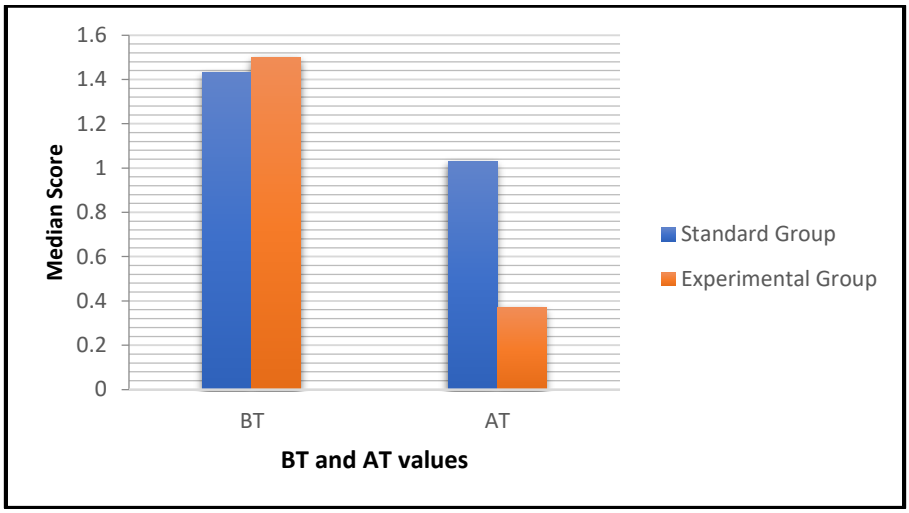


Fig.6 Assessment of Burning sensation (Daha) in Two Groups

Fig.6 As shown in the chart, the severity of the burning sensation was reduced significantly in the experimental group after taking the medication Raktapachak yoga. It needs to be improved in control group. Hence, Raktapachak yoga has shown a significant role in reducing the symptoms of urticaria (koth) caused by dooshivisha, and recurrence is also reduced.

Objective parameters

1. Haemoglobin Levels

Table 10: Statistical analysis of Haemoglobin level				
	Standard Group		Experimental Group	
Sample Size (n)	30	30	30	30
Mean ± SD	12.81 ± 1.97	12.75 ± 1.93	12.09 ± 1.63	12.28 ± 1.64
Intra-Group Comparison	Paired t test		Paired t test	
	t = 0.8297 with 29 degrees of freedom.		t = 3.298 with 29 degrees of freedom.	
P value	0.4135, considered not significant		0.0026, considered very significant	
Inter-Group Comparison	Unpaired t test			
	t = 1.011 with 58 degrees of freedom.			
P value	0.3164, considered not significant			

In Table 10, the following details are tabulated, for the standard Group, the mean haemoglobin levels before and after treatment were 12.81 ± 1.97 gm% and 12.75 ± 1.93 gm% respectively with no statistically significant difference (p = 0.4135).In the Experimental Group, the mean hemoglobin levels before and after treatment were 12.09 ± 1.63 gm% and 12.28 ± 1.64 gm%,

respectively, with statistically significant differences (p = 0.0026).The inter-group comparison showed a statistically insignificant difference between mean hemoglobin levels after treatment in the two groups (p = 0.3164).

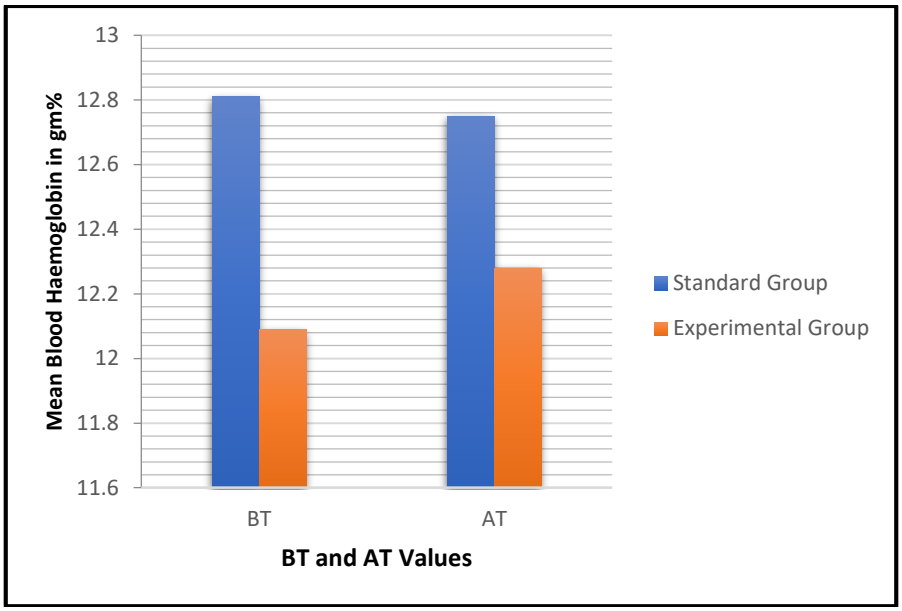


Fig.7Assessment of Blood Haemoglobin Levels in Two Groups

Fig.7- The control group did not show improvement in hemoglobin levels after medication.The experimental group showed a significant improvement in Haemoglobin levels after medication.

2. *ESR Levels*

Table 11: Statistical analysis of ESR level

	Group A		Group B	
Sample Size (n)	30	30	30	30
Mean ± SD	16.73 ± 3.82	14.23 ± 3.33	18.60 ± 6.34	13.43 ± 4.41
Intra-Group Comparison	Paired t test		Paired t test	
	t = 7.468 with 29 degrees of freedom.		t = 8.144 with 29 degrees of freedom.	
P value	< 0.0001, considered extremely significant		< 0.0001, considered extremely significant	
Inter-Group Comparison	Unpaired t test			
	t = 0.7933 with 58 degrees of freedom.			
P value	0.4308, considered not significant			

In Table 11, the following details are given. For the standard group, the mean ESR levels before and after treatment were 16.73 ± 3.82 mm/hr and 14.23 ± 3.33 mm/hr, respectively, with statistically significant differences (p < 0.0001). In the Experimental Group, mean ESR levels before and after treatment were 18.60 ± 6.34 mm/hr and 13.43 ± 4.41 mm/hr, respectively, with statistically significant differences (p < 0.0001). The inter-group comparison showed a statistically insignificant difference between mean ESR levels after treatment in the two groups (p = 0.4308).

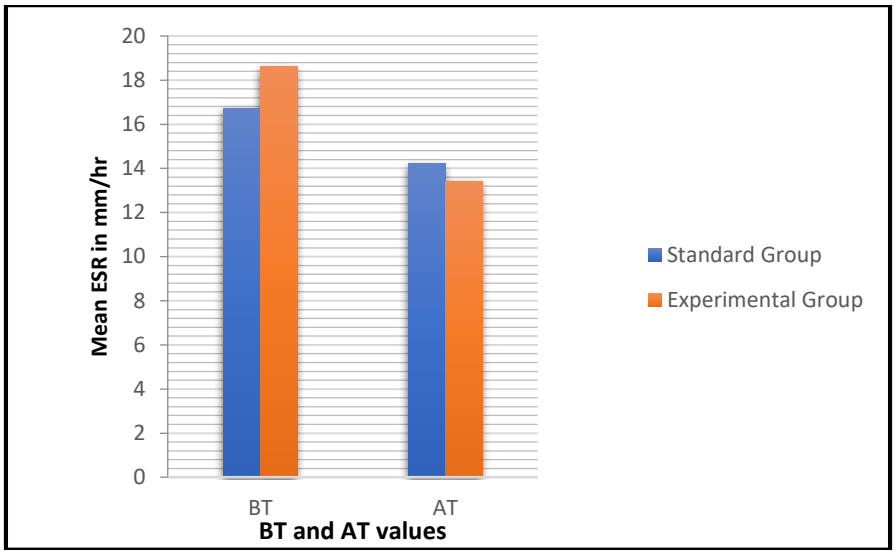


Fig 8 Assessment of ESR Levels in Two Groups

Fig 8- Both groups showed decreased ESR levels after treatment, but it is more significant in the experimental group.

3. AEC Levels

Table 12 Statistical analysis of AEC level

	Group A		Group B	
Sample Size (n)	30	30	30	30
Mean ± SD	0.43 ± 0.33	0.35 ± 0.32	0.43 ± 0.35	0.22 ± 0.17
Intra-Group Comparison	Paired t test		Paired t test	
	t = 3.434 with 29 degrees of freedom.		t = 5.577 with 29 degrees of freedom.	
P value	0.0018, considered very significant		< 0.0001, considered extremely significant	
Inter-Group Comparison	Unpaired t test			
	t = 2.019 with 58 degrees of freedom.			
P value	The two-tailed P value is 0.0481, considered significant.			

In Table 12, the following details are given for the Standard Group, the mean AEC levels before and after treatment were 0.43 ± 0.33 and 0.35 ± 0.32, respectively, with statistically significant differences (p = 0.0018).In the Experimental Group, the mean AEC levels before and after treatment were 0.43 ± 0.35 and 0.22 ± 0.17, respectively, with statistically significant differences (p < 0.0001).The inter-group comparison showed a statistically significant difference between the two groups' mean AEC levels after treatment (p = 0.0418).

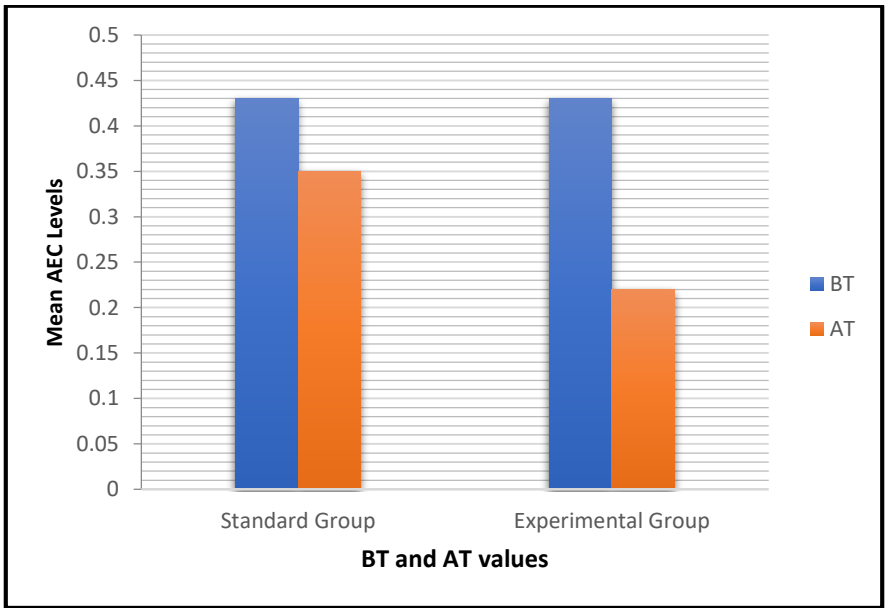


Fig.9 Assessment of AEC Levels in Two Groups

Fig9- in the standard group, there was not much decrease in AEC level compared to the experimental group. The experimental group was shown a decrease in AEC level after treatment with Raktapacak yoga.

4. Examination of Stool (ova, Parasite): Chi-square Test

Table 13 Statistical analysis of stool examination

	Before Treatment		After Treatment	
	Positive	Negative	Positive	Negative
Group A	10	20	08	22
Group B	13	17	00	30

Chi-square statistic (with Yates correction) = 5.639
Degrees of freedom = 1
The two-sided P value is 0.0176, considered significant.
The row/column association is statistically significant

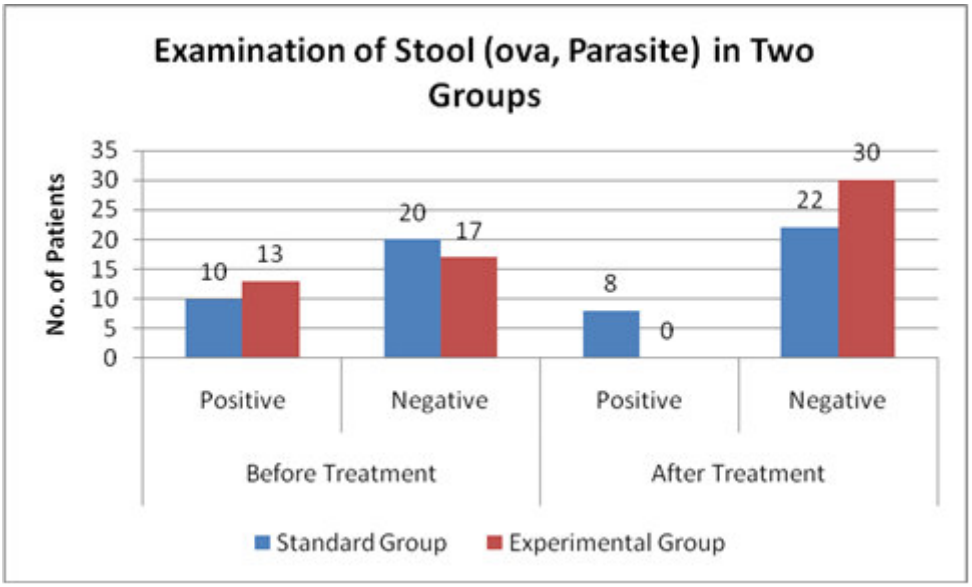


Fig. 10 Examination of Stool for presence of ova, Parasites

Fig.10- Results of stool examination for ova and parasite were negative in all experimental group patients. Objective parameters like Hb, ESR, AEC, and stool examination for ova and parasites also improved in patients with raktapachak yoga treatment. Patients from both groups had no adverse effects or reactions during a clinical trial.

Follow-up

Follow-ups of each patient from both groups were recorded regularly after 7 days up to 42 days. One patient from the standard group and one from the experimental group discontinued the follow-up. They were excluded from statistical analysis. Gradation of symptoms Koth, kandu, toda, daha was done at every 7 days follow-ups. USA scale was used. It was seen that patients from the experimental group got better relief in symptoms after ingestion of Raktapacha yoga. Objective parameters like Hb, ESR, AEC, and stool examination for ova and parasites were done before and after treatment. Objective parameters were also improved after treatment with Ratapahak yoga.

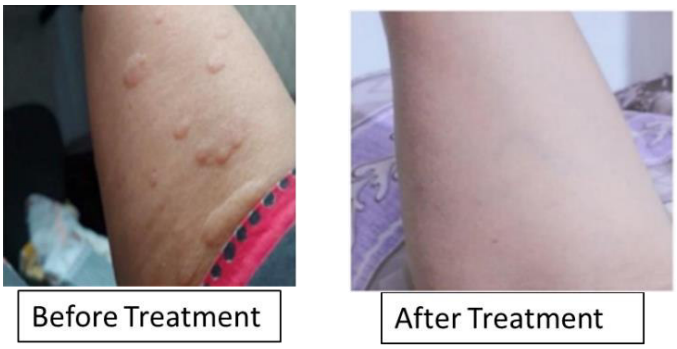


Fig.3- Images of the patient's hand before and after treatment.

5. DISCUSSION

Chronic Urticaria*(kotha)* is difficult to treat because of its incurability and recurrences[47]. In today's era due to wrong food habits and stressful lifestyle, we can find many diseases caused by dooshivisha. In dooshivisha, poison is not fully eliminated from body and shows its effects on body in favorable conditions like cumulative poisoning[48]. Food additives like preservatives, food colour and artificial sweeteners play an important role in causing chronic urticaria.[49] Chronic urticaria is also categorized as a psychodermatological disorder caused by stress.[50] Signs in dooshivisha like discoloration, altered complexion (*Vaivarnya*), swelling (shotha), red patche on skin (*mandal*), urticaria (koth) are suggestive of impurity of blood (raktavaha stroto-dushti).[51] urticaria is one of the prodromal features of skin diseases. Charkokta raktapachak yog[52] is mentioned in jwara adhikara of Charaksamhita. Jwara is a synonym of disease (vyadhi); hence, the treatment protocol given for jwara can be used for any vyadhi as per yukti pramana. So Raktapachak Yoga is useful in skin diseases (kushtha) and diseases due to impure blood like koth[53]. Many Ayurvedic formulations are described in Ayurveda for the management of Koth [54.] Some research studies of ayurvedic formulations have been done for the treatment of chronic urticaria (kotha) like Navkarshik kwatha Ghana[55], Adraka khanda [56,] treatment with multiple drugs like haridrakhanda, arogyavardhini, mahamjisthadi kwath, aragvadh vati[57.] Dooshivishari was also studied as the treatment for chronic urticaria, which has shown positive effects as a medicine for urticaria.[58] In our study, the root cause of dooshivishajanya koth i.e vitiated blood (Raktadhatu dushti) was treated with charkokta raktapachak yog to get desire result. The effectiveness of raktapachak yoga is also proven for dooshivishajanya and other skin diseases like chronic eczema (Vicharchika) [59]. Case study of kitibha kushta[60] and palmoplantar psoriasis (Vipadika kushta)[61], which were treated with raktapachak yoga with other ayurvedic formulations, also showed efficacy of raktapachak yog in the treatment of skin diseases. The controlled clinical study assessed the safety and efficacy of charkokta raktapachak yoga in the treatment of dooshivishajanya kotha with respective to Urticaria. Patients suffering from chronic urticaria for one year were included in the study. Follow up after every 7 days upto 45 days were taken regularly. Statistical analysis of subjective parameters like raised edematous swelling (kotha), itching (kandu), pricking sensation (toda), and burning sensation (daha) shows statistically significant differences in both standard and experimental groups before and after treatment. Still, the experimental group showed a more significant difference than the standard group. After giving raktapachak yoga, the frequency of episodes of urticaria(kotha) is also reduced. Objective parameters like haemoglobin, ESR, AEC and stool examination for ova and parasite are done before and after treatment for both groups. All objective parameters were statistically analyzed. The experimental group showed a better statistically significant difference in the P value. From the above-listed data, it is concluded that Charkokta Raktapachak Yoga is effective in urticaria (kotha) caused by dooshivisha. Symptoms like an edematous wheel, itching, burning sensation, and pricking sensation are relieved after treatment with raktapachak yoga. Hb level in patients is improved. Most of the ESR and AEC patients came within normal limit, Stool examination for ova showed significant results after treatment with Raktapachak yoga. The safety of Raktapachak yoga is proven as no side effects are seen in patients after Raktapachak Yoga ingestion.

6. CONCLUSION

Kotha (Urticaria) presents a prevalent health challenge marked by treatment limitations such as incurability and frequent recurrences. Ayurveda recognizes dooshivisha's impact on tridosha and raktdhatu, leading to kotha as a purvaroop of kushta (skin disease). charkokta raktapachak yoga, validated in this study, proves effective and safe in addressing dooshivishjanya kotha, particularly urticaria. Beyond immediate implications, this study explores charkokta raktapachak yoga's efficacy for other raktapradosha diseases due to dooshivisha. Future research may extend to alternative Ayurvedic medicinal yogas for dooshivisha-induced urticaria. This research advances understanding of dooshivisha's role in health and opens avenues for innovative Ayurvedic interventions. The findings contribute to holistic healthcare, aligning traditional wisdom with modern challenges and offering a promising trajectory for Ayurvedic medicine in addressing complex health issues.

7. AUTHOR'S CONTRIBUTION STATEMENT

Suvarna Kakde and Smita Patil conceptualized and designed the study. Present clinical study was done by Suvarna Kakde. Rajkumar Gupta and Pravin Kakde discussed methodology and analyzed data. All authors discussed the methodology and result and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES

1. Dr. Bramhanand Tripathi C-S, Prakashan CS, Varanasi. Chikitsasthana 23/4-6. rev ed; 2007.
2. Shastri A, Samhita S, Kalpsthana. Vol. 18. Varanasi: Choukhamba Sanskrit Sansthana [reprint]; 2007,Page-427. p. 2/17.
3. Prof Shrikantha Murthy KR, Bhavaprakasha of Bhavmishra, Krishnadas Academy, Varanasi. 1st ed, 2000. Ch67-1.
4. Sushrut Samhita of Maharshi-Sushruta edited with Ayurved Tattva Sandipika by Kaviraj Ambikadutta Shastri Forwarded by Dr. Pranajivana Manekchanda Mehta Part I. Chaukhamba Sanskrit sansthan. 14th ed: 2003, Kalpasthan chapter no 2/verse no 25-33, page 25-6.
5. Bioaccumulation - https:. Wikipedia. Wikipedia. Available from: http://en.wikipedia.org/wiki/Bioaccumulation-assessed on 22/8/20223PM.
6. Sharma RK. CharakaSamhita, Chikitsa sthana,23/31,Varanasi,Choukhamba Sanskrit Sansthana,Page-339.
7. Sushrut Samhita of Maharshi-Sushruta edited with Ayurved Tattva Sandipika by Kaviraj Ambikadutta Shastri Forwarded by Dr. Pranajivana Manekchanda

Mehta Part I. Chaukhamba Sanskrit sansthan. 14th ed: 2003, Kalpasthan chapter no 2/ verse no 30-32 page no 26.
8. Nidana M, Chapter 57, verse 1. Hindi Translation by Narendranath Shastri, Motilal banarasidas Pratisthana. Delhi. p. 638.
9. Available from: https://emedicine.medscape.com/article/762917-overview assessed on 31/10/22 3PM.
10. Losol P, Yoo HS, Park HS. Molecular genetic mechanisms of chronic urticaria. Allergy Asthma Immunol Res. *2014*;6(1)*: 1321*PMC 3881394:13-21:13-21. doi: 10.4168/aair.2014.6.1.13, PMID 24404388.
11. Sushrut Samhita of Maharshi-Sushruta edited with Ayurved Tattva Sandipika by Kaviraj Ambikadutta Shastri Forwarded by Dr. Pranajivana Manekchanda Mehta Part I. Chaukhamba Sanskrit sansthan. 14th ed: 2003, Kalpasthan chapter no 2/ verse no 53-54 page no 29.
12. Sharma RK, CharakaSamhita C. Varanasi,Choukhamba Sanskrit Sansthana,Page-343. p. 23/61-64.
13. Sharma RK. CharakaSamhita,Chikitsa sthana,3/202,Varanasi,Choukhamba Sanskrit Sansthana, Page-301.
14. Dr. Sastry JLN. illustrated *DravyagunaVijnana*: a study of the Essential Medicinal Plants in Ayurveda. 1st ed. Vol. II. Varanasi: Chaukhamba Orientalia; 1999.
15. Sharma RK. CharakaSamhita, sutra sthana,4,Varanasi,Choukhamba Sanskrit Sansthana, pages-245-253.
16. Shastri A, Samhita S, Sthana S, Varanasi CSS [reprint] 2007, pages-276-281.
17. Anonymous. Ayurvedic pharmacopoeia of India. Vol. I. New Delhi: Ministry of Family Health and Welfare. p. p. III, V.
18. Bhattacharya S, Haldar PK. Trichosanthes dioica root possesses stimulant laxative activity in mice. Nat Prod Res. 2012;26(10):952-7. doi: 10.1080/14786419.2010.535161, PMID 21827370.
19. Bhattacharya S, Haldar PK, Ghosh AK. Paralytic and lethal effects of Trichosanthes dioica root extracts in experimental worms. Pharm Biol. 2010 Sep;48(9):960-5. doi: 10.3109/13880200903111144, PMID 20695728.
20. Bhattacharya S, Haldar PK. Protective role of triterpenoid enriched extract of T. dioica root against experimentally induced pain and inflammation in rodents.
21. Kumar Rai P, Gupta SK, Srivastava A. Kumari, Gupta RK, Watal. GA Sci Validation Antihyperglycemic Antihyperlipidemic Attributes Trichosanthes dioicaISRN Pharmacol;2013:7.
22. Gayathri M, Kannabiran K. Antimicrobial activity of Hemidesmus indicus, Ficus bengalensis and Pterocarpus marsupium roxb. Indian J Pharm Sci. 2009;71(5):578-81. doi: 10.4103/0250-474X.58182, PMID 20502584.
23. Sundaram MS, Sivakumar T, Balamurugan G. Anti-inflammatory effect of Cyperus rotundus Linn. leaves on acute and subacute inflammation in experimental rat models. Biomedicine. 2008;28:302-4.
24. Gupta MB, Palit TK, Singh N, Bhargava KP. Pharmacological studies to isolate the active constituents from Cyperus rotundus possessing anti-inflammatory, antipyretic and analgesic activities. Indian J Med Res. 1971 Jan;59(1):76-82. PMID 5574385.
25. Singh N, Kulshrestha VK, Gupta MB, Bhargava KP. Pharmacological studies on Cyperus rotundus. Indian J Pharmacol. 1969;1(2):9.
26. Rem BJN. Swamy, Shivakumar & Hiremath, Suresh & Hallikeri, C.s & Hatapakki, B.C. & Handiganur, J.S. & Sankh, Kuber & Shivakumar. 2009. Anticonvulsant Effect of Cyperus rotundus Linn Rhizomes in Rats;9:192-6. doi: 10.18311/Jnr/2009/239.
27. Amresh G, Singh PN, Rao ChV. The antinociceptive and antiarthritic activity of Cissampelospareiraroots-Journal of Ethnopharmacology. J Ethnopharmacol. 2007;111(3):531-6. doi: 10.1016/j.jep.2006.12.026, PMID 17240096.
28. Amresh G, Reddy GD, Rao ChV, Singh PN. Evaluation of the anti-inflammatory activity of Cissampelos pareiraroot in rats. J Ethnopharmacol. 2007 Apr 4;110(3):526-31. doi: 10.1016/j.jep.2006.10.009, PMID 17097249.
29. Ganguly M, Borthakur Kr. M, Devi N, Mahanta R. Antifertility activity of the methanolic leaf extract of Cissampelos pareira in female albino rats. J Ethnopharmacol. 2007;111(3):688-91. doi: 10.1016/j.jep.2007.01.023, PMID 17324540.
30. Amresh G, Rao CV, Singh PN. Antioxidant activity of Cissampelos pareiraon benzo (a) pyrene-induced mucosal injury in mice. Nutr Res. 2007;27(10):625-32. doi: 10.1016/j.nutres.2007.05.009.
31. Badilla B, Chaves F, Jimenez S. Effects of an extract of Cissampelos pareiraon the hemorrhagic and proteolytic activities from Bothrops asper venom. Pharmacogn Mag. 2008;4:27-31.
32. Zhang DK, Yu JJ, Li YM, Wei LN, Yu Y, Feng YH, et al. A Picrorhiza kurroa Derivative, picroliv, Attenuates the Development of dextran-SulfateSodium-Induced Colitis in Mice. Mediators Inflamm. 2012;2012:751629. doi: 10.1155/2012/751629, PMID 23125487.
33. Dorsch W, Stuppner H, Wagner H, Gropp M, Demoulin S, Ring J. Antiasthmatic effects of Picrorhiza kurroa: androsin prevents allergen and PAF-induced bronchial obstruction in guinea pigs. Int Arch Allergy Appl Immunol. 1991;95(2-3):128-33. doi: 10.1159/000235416, PMID 1718906.
34. Rajeshkumar NV, Kuttan R. Protective Effect of picroliv, the Active Constituent of Picrorhiza kurroa, Against Chemical Carcinogenesis in Mice. Teratog Carcinog Mutagen. 2001;21(4):303-13. doi: 10.1002/tcm.1018, PMID 11406836.
35. Kumar PV, Sivaraj A, Madhumitha G, Saral AM, Kumar BS. In vitro antibacterial activities of Picrorhiza kurroa rhizome extract using agar well diffusion method. Int J Curr Pharm Res. 2010;2(1):30-3.
36. Gupta A, Khajuria A, Singh J, Bedi KL, Satti NK, Dutt P, et al. Immunomodulatory activity of biopolymeric fraction RLJ-NE-205 from Picrorhiza kurroa. Int Immunopharmacol. 2006;6(10):1543-9. doi: 10.1016/j.intimp.2006.05.002, PMID 16919826.
37. Sharma RK. CharakaSamhita,Chikitsa sthana,3/200-203,Varanasi,Choukhamba Sanskrit Sansthana, Page-301.
38. BhavprakashNighantu. By Acharya Bhava Mishra With Hindi commentary by K-Chunekar 7th Edi,Chaukhambha. Varanasi: Amara Bharati Academy; 1986.

39. Available from: https://www.mdcalc.com › calc › urticaria-activity-score. Asssed on 31/12/2023. 1:00PM.
40. Assessed on 31/12/2022;1:20PM.
41. Available from: https://pubmed.ncbi.nlm.nih.gov. Assessed on 31/12/2022. Vol. 2. 00 PM.
42. Available from: https://www.statisticshowto.com/probability-and-statistics/statistics-definitions/wilcoxon-signed-rank-test/Assessed on 31/12/2022;3:20 PM.
43. Available from: https://sixsigmastudyguide.com/mann-whitney-non-parametric-hypothesis-test/Assessed on 31/12/2022 3:45PM.
44. BK Mahajan methods in biostatistics, Chapter 9. Jaypee brothers Medical Publishers Ltd. In:. 6th ed; 2006, Page-147.
45. BK Mahajan methods in biostatistics, Chapter 9. Jaypee brothers Medical Publishers Ltd. In:. 6th ed; 2006, Page-142.
46. BK Mahajan methods in biostatistics, Chapter 11. Jaypee brothers Medical Publishers Ltd. In:. 6th ed; 2006, Page-168.
47. Available from: https://www.sciencedirect.com/science/article/abs/pii/S2213219817305378 assessed on 31/12/2022 3:00 PM.
48. Pradeep Patil et.al. Conceptual Study of Dooshivisha (Cumulative toxicity). Journal of Ayurveda and integrated medical sciences | Sep - Oct 2016 | Vol. 1 | Issue 3, p-149.
49. Sahu SC. Food additives: a special issue of the journal Food and Chemical Toxicology. Food Chem Toxicol. 2017;107(B):529. doi: 10.1016/j.fct.2017.05.018, PMID 28501486.
50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5949545/assessed o 31/12/2022;3:30 PM.
51. Shastri A, Samhita S, Varanasi SK. Choukhamba Sanskrit Sansthana [reprint]; 2007. p. 2/30-32, Page-423.
52. Sharma RK. CharakaSamhita,Chikitsa sthana,3/202,Varanasi,Choukhamba Sanskrit Sansthana, Page-301.
53. Mishra BR, Dhatupachak Yoga A. Int J Res Indian Med. 2018;2(1):1-8.
54. Dr.vandana chandel. International Research journal of Ayurveda and Yoga, IJRAY. Vol. 2(2, Mar-Apr); 2019. p. 57-63.
55. Rathod R, Thakre PP, Ade V. Evaluation of efficacy of Navakarshik Kwath Ghan in Sheetpitta WSR to urticaria. IJAM;11(3):441-5. doi: 10.47552/ijam.v11i3.1624.
56. Chavhan NS, Rathi B. Pharmaceutico-analytical study of Adraka Khanda. J Indian Sys Medicine. 2019;7(2):112-8. doi: 10.4103/JISM.JISM_19_19.
57. Shere A, Meenakshi R-K. Ayurvedic management of Shitpitta W.S.R. To urticaria- A Case Report, IAMJ August 2021, page-1896.
58. Priti L et al. Dooshivishari agada in Kotha (urticaria). J Indian Syst Vol. Apr-Jun 2018, Page-50.
59. European. J Mol Clin ISSN 2515. 2018;8260;05(1):447-53.
60. Avhad MR. Ayurvedic management of kitibha kushta- a case study. Ayurlog N Atl J Res Ayurved Sci. Apr 2020;8(02):2020;8,page-01-03.
61. Gabhane SM. Ayurvedic management of Vipadika Kushtha (palmoplantar psoriasis) – A single case study, IJCRR - 13. 2021;4(Feb):171-5.