The effect of T.Cordifolia and Z.Officinale in the Treatment of Rheumatoid Arthritis

Amrit Godbole[1*], KM Sweta[2], O. Abhinav[3], O.P. Singh[4]

[1] *Senior Resident Department of Kayacikitsa, Faculty of Ayurveda, IMS BHU, Varanasi, India*
[2] *Assistant Professor, Department of Rachana Sharir, AIAMS, Chunar, Mirzapurr, India*
[3] *Assistant Professor (Panchakarma), Department of Kayacikitsa, Faculty of Ayurveda, IMS BHU, Varanasi, India*
[4] *Professor Department of Kayacikitsa, Faculty of Ayurveda, IMS BHU, Varanasi, India*

ABSTRACT

Background: Rheumatoid arthritis (RA) is emerging as a prevalent disorder with a higher rate of complications, morbidity, and mortality. This highlights the need for Ayurvedic medicines for reducing the impact of RA. **Aims and Objective:** To study the effect of 3-month treatment of *Guduchi Ghan Vati* (Aqueous extract of Tinospora cordifolia) and *Sunthi churna* (Zingiber officinale powder) along with *Virecana Karma* (medicated purgation) in patients with RA. **Material and Methods:** 40 patients of age group 20-60 years, of either sex meeting the European League Against Rheumatism (EULAR) criteria of RA were randomly divided into two groups, Control and Intervention. The intervention group received *Virecana* (medicated purgation) followed by *Guduchi Ghan Vati* (Aqueous extract of Tinospora cordifolia) 4 tab TDS (1 tab= 500 mg), *Sunthi churna* (Zingiber officinale powder) 5g BD, while the control group was given Tab. Etoricoxib at a fixed dose of 90 mg OD for 90 days. All participants gave written informed consent. An assessment was done by improvement in chief complaints and biochemical parameters (RA-titre, CRP, Anti-CCP titers and TNF-alpha) at baseline and at the end of 12 weeks. Adverse events and drug tolerability were analyzed. **Results**: Clinical symptoms and biochemical parameters were significantly reduced from beginning to end of the treatment (P<0.001). **Conclusions**: The study provided good evidence in support of the efficacy and safety of *Virecana Karma* (medicated purgation) followed by *Guduchi Ghan Vati* (Aqueous extract of Tinospora cordifolia) and *Sunthi churna* (Zingiber officinale powder) in the management of Rheumatoid arthritis.

Key Words: *Rheumatoid Arthritis; Guduchi Ghan Vati; Sunthi churna; Virecana; Amavata.*

eIJPPR 2019; 9(4):1-9

HOW TO CITE THIS ARTICLE: Godbole A, Sweta, KM, Abhinav O., Singh O.P. (2019). The effect of T.Cordifolia and Z.Officinale in the treatment of rheumatoid arthritis, Int. j. pharm. phytopharm. res, 9(4), pp.1-9.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory systemic, chronic, disorder with an unknown reason that mainly involves joints but it can cause multiple extra-articular manifestations, too [1]. RA is the most prevalent autoimmune disease that affects 1–1.5% of the people around the world [2, 3]. The joint injury was seen to be associated with the early feature of the illness [4, 5].

The age of onset is usually around the 30s with the peak in the 50th decade of life. RA with disease onset at ages below 65 years is called Young-Onset RA (YORA) while RA starting at ages over 65 is called Late-Onset RA (LORA). The prevalence increases with age, and gender differences diminish in the older age group [6].

symmetrical peripheral inflammatory polyarthritis that results in joint destruction and will be related to extra-articular manifestations [7]. The etiology and multiple lifestyle and environmental factors are associated with it [8].

well understood. The joint damage, swelling, and synovitis, characterizing active RA are the final results of inflammatory processes and complex autoimmune that involve components of both the adaptive and innate immune systems. In a prone individual, the interaction of environment and genes results in a loss of tolerance of self-proteins that contain a citrulline residue. These proteins are produced by post-translational modification of arginine to citrulline by the enzyme peptidyl arginine

Corresponding author: Amrit Godbole
Address: Senior Resident Department of Kayacikitsa, Faculty of Ayurveda, IMS BHU, Varanasi 221005.
E-mail: ✉ amritgodbole2 @ gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 23 March 2019; **Revised:** 03 August 2019; **Accepted:** 15 August 2019

deiminase [9].

Prostaglandin E2 increases the production of interleukin-4 and decreases the formation of interleukin-1, interleukin-2, and TNF-α, which can be a reason for autoimmune disorders including rheumatoid arthritis [10].

NSAIDs are the most commonly used substances for symptomatic treatment. NSAIDs are effective analgesic and anti-inflammatory drugs, which can inhibit the biosynthesis of prostaglandin at the level of cyclooxygenase enzyme (COX) [11, 12].

NSAIDs are also related to several gastrointestinal issues, ranging from mild to severe dyspeptic symptoms, the development of duodenal or gastric ulceration, perforation or hemorrhage, and other events that may lead to death or hospitalization [13].

Nowadays the use of alternative therapies, including medicative herbs and acupuncture is growing and according to reports, about 60-90% of dissatisfied arthritis patients are likely to use the complementary and alternative medicine (CAM) approach to overcome pain and related problems [14].

nti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) are autoantibody systems that are most commonly used to classify/diagnose RA. They are the prelude to the onset of symptoms of the disease and predict a more severe course of it, playing a pathogenic role in RA. Therefore, they promote a lot of accurate prognoses and contribute to much better illness management. Their importance has recently been emphasized by the insertion of ACPA alongside the previously included RF on EULAR RA diagnostic criteria [15].

MATERIAL AND METHODS

Objective the aim of the present study was to evaluate the safety and efficacy of *Virecana Karma* (Medicated purgation) followed by *Guduchi Ghan Vati* (Aqueous extract of Tinospora cordifolia) and *Sunthi churna* (Zingiber officinale powder) by evaluating improvements in chief complaints and biomarkers. This investigation was carried out according to Indian Council of Medical Research (ICMR) ethical guidelines for biomedical research adopted from World Medical Association (WMA) – Declaration of Helsinki on human participants and Schedule Y of Drugs and Cosmetics Act, India, amended in 2005. The patients attending the outpatient department of the institute participated in the study. Method of drug administration for *Virecana karma* was shown [Table 1].

Table 1. Method of drug administration for Virechana karma

S.No	Procedure	Drug & dose	Duration
1.	**Dipana – Pacana**	Trikatu churna 3g TDS with warm water (half an hour before meal)	3 days
2.	**Snehapana**	Pancatikta-Ghrita starting from 30 ml with a daily increment of 30 ml till Samyak Snehana.	7 days
3.	**Abhyanga & svedana**	Mahanarayana Tail once daily	3 days
4.	**Virecana Karma**	Trivritta Leha 50-100g with ushnodaka (depending on the condition)	On the day of Virechana
5.	**Sansarjana Karma**	Diet as per shuddhi	7 days

Patients

40 patients of either sex, diagnosed for RA as per EULAR (The European League against Rheumatism) criteria were recruited from patients visiting the outpatient department of *Kayacikitsa*, Sir Sunder Lal Hospital, IMS-BHU, Varanasi, India.

Washout period

a two-week washout period only if the patients give the previous history of taking Ayurvedic/Allopathic/any medicine (any local or oral application was gradually withdrawn within 1 week and the subject did not give any medicine for the next week and then he/she was registered for the trial).

Subjects of the age range of 20-60 years of either sex, willing to participate in the investigation for twelve weeks, and diagnosed as per EULAR diagnostic criteria with symptoms of RA were included in the study.

Exclusion Criteria:

patients with psoriatic arthritis, osteoarthritis, and gouty arthritis, history of a fractured joint or trauma, and surgical history to the joint in last 6 months were not included in the study. Furthermore, patients with gross disability in their daily routines such as confined to a wheelchair or bedridden subjects, prolonged (more than 6 weeks) medication with corticosteroids, uncontrolled type2 diabetes, uncontrolled hypertension (higher than 160/100 mmHg), any deformity of knee, hip or back altering the posture and gait, , antidepressants, anticholinergics, past history of atrial fibrillation, acute coronary syndrome, myocardial infarction, stroke or severe cardiac arrhythmia within the last six months, severe nephritic or hepatic disorders, and pregnant and lactating ladies were additionally excluded from the study.

Withdrawal criteria

The subjects were free to withdraw from the experiment whenever they wanted, without the permission of the investigator or any reason. Furthermore, if the treatment was not followed or any side effects occurred (At least 80% compliance was necessary to continue the study), the investigator could discontinue the subject. In these cases, steps are taken to inform the reasons for the withdrawal and were recorded in the case report forms.

Screening Methods

All patients included in this study were thoroughly examined and data were recorded systematically. Laboratory investigations were carried out at Clinical Laboratory, IMS BHU, Varanasi, in all patients at baseline and on 90th day of the intervention.

Study design

The study was an intervention-controlled, randomized, and prospective trial with 1:1 participants assigned to 2 groups. The scholars who were involved in administration distribution, and randomization of the articles were independent of the investigators. Random numbers generated by computer were used in the study. Block size was four. The patients were divided into intervention and control groups with an equal proportion. Based on mean difference and Standard Deviation of the difference of Baseline and post-study of RA titer (66.30±76.20) of the previous study conducted on the similar subject, the calculated sample size is n=16 further assuming 20% loss to follow up the required sample size is 20 in each group. Therefore, 40 patients were enrolled for the study among which 8 patients declined to participate at different points of time in the trial. (Fig.1. flow chart of participants)

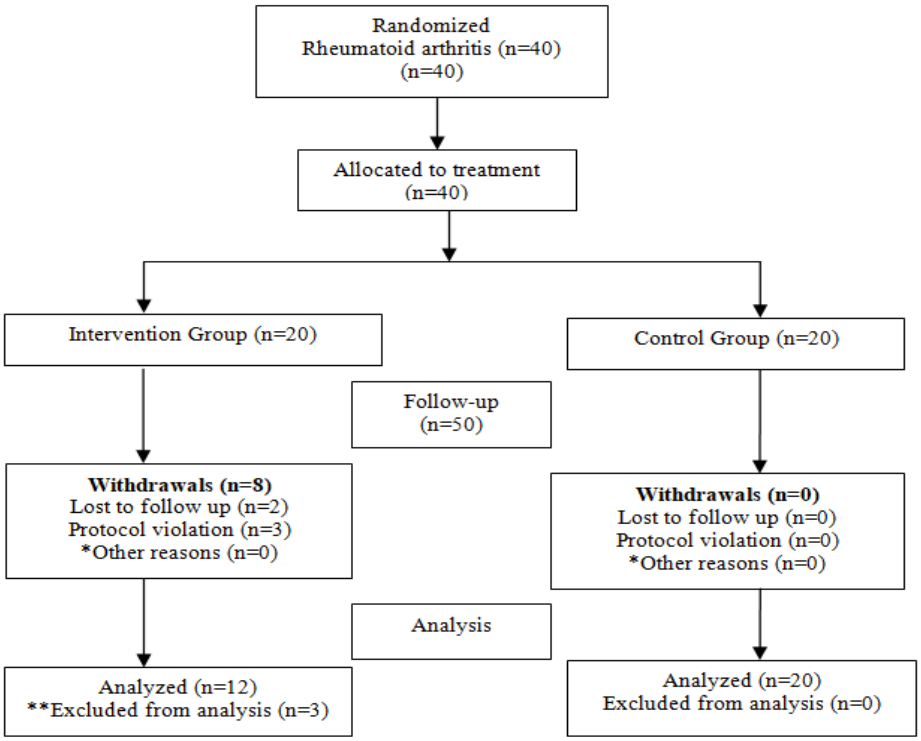

Figure 1. Participant flow chart

*Other reasons include non-compliance and migration of patient to a distant location. **Patients did not report for follow-up after randomization.

Intervention

All the patients were randomly divided into 2 groups: Control and Intervention. The intervention group (n=20) received *Virecana Karma* followed by *Guduchi Ghan Vati* (Aqueous extract of Tinospora cordifolia) [16] and *Sunthi* (Zingiber officinale powder), while the control group (n=20) received Tab. Etoricoxib at a fixed dose of 90 mg OD for 90 days.

Interventions were from classical textbooks of *Ayurveda*. The intervention dose was according to classical studies. All drugs were procured from the Ayurvedic Pharmacopoeia of India (API) complied GMP (Good manufacturing practice) certified company. [17] The intervention duration was 90 days with follow-up on every 30 days. The nature and design of the investigation were explained to patients, and informed consent was obtained. The study was authorized by the Institutional Ethics Committee (Protocol Id ECR/526/Inst/UP/2014 was approved by the Institutional Human Research Ethics Committee of Banaras Hindu University, IMS, Varanasi, Date of Approval 21.03.2015). Data collection was from March 2016 to February 2017. During the study, it was asked from the patients to adhere to the treatment protocol and report any effects as quickly as possible to the

investigators. During the intervention, the investigators screened any new or existing manifestations leading to significant distress, for possible adverse events.

Criteria for assessment

Primary Outcomes:

Chief complaints were primary outcomes.

Secondary Outcomes:

The secondary outcomes were RA factor, CRP, Anti CCP, and TNF-alpha, recorded by following the standard operating procedures.

Blinding and masking

Double-blinding was not possible because this was an interventional study. The Proforma was coded and analyzed only after the study completion. The statistician who did the randomization and data analysis was blinded to the treatment status of the individuals.

Statistical methods

The analysis of the data using SPSS software 20.0 (IBM Corp. Released 2011. IBM SPSS 20.0. Armonk, NY: IBM Corp) describing quantitative measures are expressed as median or mean ± SD or SE or the mean with range. Qualitative variables are presented as counts and percentage. Comparison of variables representing categorical data was performed using the Chi-square test. All p (probability) values were reported based on two-sided significance test and all the statistical tests were interpreted as significance at 5% level ($p < 0.05$)

RESULTS

A total of 40 patients participated in the study. No patients in either group reported any adverse effects.

Patients Characteristics

In this study, patients with age ranges of 31-40 and 41-50 were more affected (26.66% and 41.66% respectively). Furthermore, most of the subjects (70%) had tea/coffee addiction; 53.33% had constipated bowel habit; The onset of disease was found insidious in 71.66%; 50% were housewives; 45% were in middle economic status and 23.33% in a lower class; 33.33% had the illness duration of 3-4 years and 30% between 1-2 years; 70% of patients did not have any positive family history. There were not any significant changes at the end of treatment from baseline in the vital signs i.e. pulse rate, Respiratory rate, diastolic and systolic blood pressure, appetite, and body weight.

Primary outcome

Significant A significant improvement was found in the cases between the pre- and post-treatment in various symptomatic domains in yoga group individuals.

In the intervention group, 66.70% of cases had a severe-to-extreme grade of pain before treatment, which decreased in successive follow-ups, and in the 3rd follow-up, 75% belonged to no pain to a mild grade of pain. Statistically, both groups were found significant ($p<0.001$) There was not any significant difference between groups after completion of the treatment (because p was >0.05 in both cases) but the intervention group showed the highest percentage of cured subjects [Table 2].

Table 2. Pain assessment in both groups at baseline and post-study

Grade	Pain			
	Intervention Group		Control Group	
	Baseline (%)	Post study (%)	Baseline (%)	Post study (%)
0 (Absent)	0(0%)	2(16.7%)	0(0%)	0(0%)
1 (Mild)	0(0%)	7(58.3%)	2(10%)	11(55%)
2 (Moderate)	4(33.33%)	2(16.7%)	8(40%)	5(25%)
3 (Severe)	6(50.0%)	1(8.3%)	7(35%)	3(15%)
4 (Extreme)	2(16.7%)	0(0%)	3(15%)	1(5%)
Intragroup comparison (Friedmans test)	$\chi^2 = 29.06$ p = 0.000		$\chi^2 = 24.140$ p = 0.000	
Intergroup comparison (Mann-Whitney test)	z= 0.91 p= 0.36		z=1.60 p= 0.11	

In both control and intervention groups, the initial percentage of cases with no symptom was 0%, which respectively became 20% and 50% after the 3rd follow-up and is statistically significant ($P<0.001$). There was not any significant difference between the groups ($p>0.05$). [Table 3].

Table 3. Tenderness assessment in both groups at baseline and post-study

Grade	Tenderness			
	Intervention Group		Control Group	
	Baseline (%)	Poststudy (%)	Baseline (%)	Post study (%)
0 (Absent)	0(0%)	6(50%)	0(0%)	4(20%)

ISSN (Online) 2249-6084 (Print) 2250-1029

1 (Mild)	0(0%)	3(25%)	1(5%)	6(30%)
2 (Moderate)	5(41.7%)	2(16.7%)	9(45%)	4(20%)
3 (Severe)	7(58.3%)	1(8.3%)	10(50%)	6(20%)
Intragroup comparison (Friedmans test)	$\chi^2 = 22.6$ p = 0.000		$\chi^2 = 16.59$ p = 0.001	
Intergroup comparison (Mann-Whitney test)	z = 0.55 p = 0.57		z = 1.85 p = 0.06	

Observation in the intervention group shows that the number of cases with absence of swelling was 0% initially which became 50% after the 3rd follow-up, which is statistically significant (P<0.001); in the control group, the number of cases with the absence of symptom in the 3rd follow-up remained the same with some improvement, which is also statistically significant (P<0.05). There was not any significant difference between the groups (p>0.05) [Table 4].

Table 4. Swelling assessment in both groups at baseline and post-study

Grade	**Swelling**			
	Intervention Group		**Control Group**	
	Baseline	**Post-study**	**Baseline**	**Post-study**
0 (Absent)	0(0%)	6(50%)	0(0%)	0(0%)
1 (Mild)	1(8.3%)	3(25%)	1(5%)	10(50%)
2 (Moderate)	6(50%)	2(16.7%)	10(50%)	7(35%)
3 (Severe)	5(41.7%)	1(8.3%)	9(45%)	3(15%)
Intragroup comparison (Friedmans test)	$\chi^2 = 24.51$ p = 0.000		$\chi^2 = 15.74$ p = 0.001	
Intergroup comparison (Mann-Whitney test)	z = 0.26 p = 0.79		z = 2.43 p = 0.015	

In the intervention group, the severity of stiffness decreased with each follow-up. Initially, the number of cases with absence of symptom was 0%, which became 41.70% after the 3rd follow-up, which is statistically significant (P<0.001) while it was insignificant in the control group. There was not any significant difference between the groups (p>0.05) [Table 5].

Table 5. Stiffness assessment in both groups at baseline and post-study

Grade	**Stiffness**			
	Intervention		**Control**	
	Baseline	**Post-study**	**Baseline**	**Post-study**
0 (Absent)	0(0%)	5(41.7%)	0(0%)	2(10%)
1 (Mild)	2(16.7%)	4(33.3%)	2(10%)	9(45%)
2 (Moderate)	4(33.3%)	1(8.3%)	9(45%)	6(30%)
3 (Severe)	6(50%)	2(16.7%)	9(45%)	3(15%)
Intragroup comparison (Friedmans test)	$\chi^2 = 16.807$ p = 0.001		$\chi^2 = 12.194$ p = 0.007	
Intergroup comparison (Mann-Whitney test)	z = 0.04 p = 0.96		z = 1.55 p = 0.12	

Secondary outcomes

The pre- and post-intervention assessments were carried out by evaluating biochemical profiles. Mean± SD was used to assess the effect of treatment through the outcome from baseline to the 90th day (FU-3). In the treatment analysis, the participants in the intervention group showed greater improvement than the participants in the control group (P<0.05) [Table 6].

Table 6. Biochemical assessment in both groups at baseline and post-study

Biochemical profiles	**Intervention Group**		**Control Group**	
	Baseline Score (Mean ± SD)	**Follow up score (Mean ± SD)**	**Baseline Score (Mean ± SD)**	**Follow up Score (Mean ± SD)**
RA Factor	49.04 ± 23.33	37.91 ± 6.71	42.95 ± 21.21	38.96 ± 29.01

CRP	11.01 ± 6.18	6.07 ± 4.22	11.15 ± 5.89	8.60 ± 3.54
Anti ccp	59.04 ± 27.74	37.90 ± 19.56	54.69 ± 27.37	50.26 ± 26.15
TNF-alpha	22.50 ± 11.02	15.65 ± 8.75	21.32 ± 8.57	14.87 ± 7.30

DISCUSSION

This was a randomized controlled prospective study of assessing the efficacy of *Virecana karma* (purgation) along with with *Guduchi Ghana vati* and *Sunthi churna* for 12 weeks on 40 subjects diagnosed with RA in comparison to tab Etoricoxib. Results of the study showed that 41.66% of subjects had the age range of 41-50 years old. The results were statistically highly significant ($p<0.001$) and encouraging at the end of the study. The mean changes in biochemical parameters decreased in every follow-up visit. The percentage of changes in subject of chief complaints significantly decreased compared to their baseline values. Findings showed that the combination of Ayurvedic drugs reduced joint pain; joint tenderness; joint stiffness; joint swelling; and improved physical function [Tables 1, 2, 3, 4]. Baseline to end of the study values was observed in safety laboratory parameters including RA factor, CRP, Anti–CCp, and TNF alpha. No change was observed in the X-ray of joints.

, joint pain and tenderness relief were found statistically significant in both groups ($p <0.001$). However, the relief was 74.7% and 45% in the intervention and control groups, respectively. (Tables 1, 2). Relief in joint swelling was significant in both groups ($p<0.001$). The improvement percentage was 45% and 66.4% in the control and intervention groups, respectively (Table 3). In the case of joint stiffness, the intervention group showed a significant improvement of 58.1%, whereas it was 45% in the control group ($P<0.05$) (Table 4).

Mean changes in RA factor after treatment was found 22.68 % and 9.3 % in intervention and control groups, respectively, which was statistically significant ($p<0.001$) in both groups (Table 6). In the acute phase, RA factor fluctuates but in chronic conditions, it becomes stable for long duration and needs a long-term treatment to reduce the value. Mean changes in CRP (Table.6.) after treatment was 44.82% and 22.89% in the intervention and control groups, respectively. The CRP level in RA is frequently used along with the assessment of articular tenderness and swelling to estimate the disease activity level [19]. Mean changes in Anti-CCP (Table 6) after treatment was 35.8% and 8.1 % in intervention and control groups, respectively. Mean changes in TNF-alpha (Table 6) after treatment was 30.43% and 30.22 % in the intervention and control groups, respectively. The results were found statistically significant in both groups.

Basically optimal management of RA is required within 3-6 months after the onset of the disease since substantial irreversible joint damage has been shown to occur within the first 2 years. Therefore, reliable outcome and biomarker measures are necessary to evaluate the prognosis, establish an early detection, and achieve better management of the disease [20, 21].

The present study on the basis of observation & results shows that trial formulations are significantly efficacious in patients of RA but the effect is enhanced by *Virecana therapy*. After the *Virecana karma* increased immunity was observed and relief was noted [22].

Ayurvedic medicinal plants have shown significant biological effects, in particular, anti-inflammatory and immunomodulatory effects that are potentially useful and suitable for the treatment of chronic musculoskeletal disorders [23].

Tinospora cordifolia (Willd.) Miers (family Menispermaceae), [24] an important medicinal plant also known as *Guduchi*, is used for its immunomodulatory and anti-inflammatory actions [25-34]. The whole of the plant is medicinally used, but the Ayurvedic Pharmacopoeia of India has approved the use of stem as a medicine. This is due to higher alkaloid content in the stems than in the leaves [35]. *Guduchi Ghana* [36] (a concentrated form of decoction) is the secondary Kalpana (formulation) derived from the primary *Kalpana*, i.e. *Kwatha* (decoction) that is obtained from the aqueous extract of the stem of *Guduchi* (Tinospora cordifolia Miers). Many investigations have been conducted to evaluate the anti-inflammatory activity of the decoction [37], alcohol extracts [38], and water extract of the stem of *Guduchi* (T. cordifolia that grows on Azadirachta indica) [39-42]. The water extract of the T.cordifolia is found to be more potent than any other extracts [43]. Therefore, it has been planned to compare the anti-inflammatory effect of the market sample and classically prepared of *Guduchi Ghana vati*. It improves acute inflammation by inhibiting fluid exudation [44]. An analgesic effect of T. cordifolia has also been reported in investigations [45].

discovered the anti-inflammatory activity of Zingiber officinalis in 1982 [46]. They found that the anti-inflammatory activity of Zingiber (ginger) is through inhibiting prostaglandins and also leukotriene biosynthesis [47]. Young et al. studied the analgesic and anti-inflammatory effects of 6-gingerol, a main phytochemical constituent in Zingiber officinale [48].

Haghighi et al. compared the anti-inflammatory effect of ginger with ibuprofen (a commercially available anti-inflammatory medicine that is prescribed for arthritis) [49]. Both of them exhibited a similar anti-inflammatory effect, showing ginger as an effective and potential anti-

inflammatory agent. R.D. Altman et al. reported that the effect of NSAIDs on the inflammatory process is mainly caused by inhibiting the synthesis of prostaglandin. Contrary to this, ginger extract is a complex mixture that reduces inflammation through inhibiting the prostaglandin synthesis, decreasing the production of TNF-α, and inhibiting lipo-oxygenase. The current injectable protein therapies have limitations and risks and oral, small molecules like ginger that regulate TNF-α biology can replace them or provide better control of disease either alone or with existing therapies [50].

ThusThus, the study shows that the trial formulation of *Guduchi Ghana Vati* and *Sunthi churna* is effective for RA. However, it shows better results when given along with *Shodhana karma* (purification therapy) in the form of *Virecana Karma* (medicated Purgation). For evaluation of the drugs' safety, laboratory studies i.e. CBC, Hb%, ESR, Renal Function Test (RFT), Liver Function Test (LFT) were performed at baseline and at the end of the 90th day. No adverse effect was observed during the study.

CONCLUSION

It was concluded that the aqueous extract of *tinospora cordifolia* and *zingiber officinale* powder along with medicated purgation (virecana) was effective for Rheumatoid arthritis. RA is a genetic and autoimmune disease in origin; so, the complete remission is not possible. The general quality of life was found to be more improved in patients of the intervention group because of the combination of *Virecana Karma* (medicated purgation) with the trial drugs. This prospective study provided some evidence in support of the safety and efficacy of Ayurvedic medicines. It is an effective and safe way to treat RA.

Consent for publication: This manuscript does not include details, images, or videos relating to an individual person, thus no informed consent was required.

Sources of funding

None.

Conflict of interest

None.

ACKNOWLEDGMENTS

We thank Prof. Girish Singh (Dept. of Community Medicine) and Prof. S. P. Mishra (Department of Biochemistry) for their valuable supports..

REFERENCES

[1] Khoja SO, Al-Jehani RF, Bahlas SM, Algamdi SA, Attar S. Evaluatıon of Relatıonshıp between Vıtamın D Receptor Gene Polymorphısms and Rheumatoıd Arthrıtıs in Saudı Populatıon. Pharmacophore. 2018 Jan 1;9(1):85-94.

[2] Wolfe AM, Kellgren JH, Masi AT. The epidemiology of rheumatoid arthritis: a review. II. Incidence and diagnostic criteria. Bulletin on the rheumatic diseases. 1968 Nov;19(3):524-9.

[3] Wood JW, Kato H, Johnson KG, Uda Y, Russell WJ, Duff IF. Rheumatoid arthritis in Hiroshima and Nagasaki, Japan prevalence, incidence, and clinical characteristics. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1967 Feb;10(1):21-31.

[4] Heijde DM, Leeuwen MA, Riel PL, Koster AM, Hof MA, Rijswijk MH, Putte LB. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1992 Jan;35(1):26-34. [PubMed]

[5] Deodhar AA, Brabyn J, Jones PW, Davis MJ, Woolf AD. Longitudinal study of hand bone densitometry in rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1995 Sep;38(9):1204-10.[PubMed]

[6] Amaya-Amaya J, Rojas-Villarraga A, Mantilla RD, et al. Rheumatoid arthritis. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 24. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459454/

[7] Raza K, Buckley CE, Salmon M, Buckley CD. Treating very early rheumatoid arthritis. Best practice & research Clinical rheumatology. 2006 Oct 1;20(5):849-63. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3145120/

[8] Xu, B., & Lin, J. (2017). Characteristics and risk factors of rheumatoid arthritis in the United States: an NHANES analysis. PeerJ,5,e4035. doi:10.7717/peerj.4035 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5703145/

[9] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Eng J Med. 2011;365(23):2205-2219.

[10] Tsvetkova DD, Ivanova SA. GC Determination of Fatty Acids in Fish Supplements. Internatıonal Journal of Pharmaceutıcal Research and Allıed Scıences. 2018 Jan 1;7(3):153-65.

[11] Crofford LJ. Use of NSAIDs in treating patients with arthritis. Arthritis research & therapy. 2013 Jul;15(3):S2.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891482/

[12] Cinthura C, Thangavelu L, Roy A. COX2 Inhibitory Activity of Abutilon Indicum. International Journal of Pharmaceutical Research & Allied Sciences. 2018 Oct 1;7(4).

[13] Russell RI. Non-steroidal anti-inflammatory drugs and gastrointestinal damage—problems and solutions. Postgraduate medical journal. 2001 Feb 1;77(904):82-8. https://pmj.bmj.com/content/77/904/82

[14] https://www.sciencedirect.com/science/article/pii/S0975947616304235

[15] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010 Sep;62(9):2569-81.

[16] Radner H, Neogi T, Smolen JS, Aletaha D. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Annals of the rheumatic diseases. 2014 Jan 1;73(1):114-23. https://doi.org/10.1136/annrheumdis-2013-203284. [PubMed]

[17] Szodoray P, Szabó Z, Kapitány A, Gyetvai Á, Lakos G, Szántó S, Szücs G, Szekanecz Z. Anti-citrullinated protein/peptide autoantibodies in association with genetic and environmental factors as indicators of disease outcome in rheumatoid arthritis. Autoimmunity reviews. 2010 Jan 1;9(3):140-3..

[18] Farid SS, Azizi G, Mirshafiey A. Anti-citrullinated protein antibodies and their clinical utility in rheumatoid arthritis. International journal of rheumatic diseases. 2013 Aug;16(4):379-86.

[19] https://www.ncbi.nlm.nih.gov/pubmed/27833370

[20] Chopra A, Saluja M, Tillu G, Venugopalan A, Sarmukaddam S, Raut AK, Bichile L, Narsimulu G, Handa R, Patwardhan B. A randomized controlled exploratory evaluation of standardized Ayurvedic formulations in symptomatic osteoarthritis knees: a Government of India NMITLI Project. Evidence-based complementary and alternative medicine. 2011;2011. https://doi.org/10.1155/2011/724291.

[21] Krishnamurthi A. The Wealth of India: Raw Materials: Vol. VIII. Ph-Re. The Wealth of India: Raw Materials: Vol. VIII. Ph-Re.. 1969;251.

[22] Rai M, Gupta SS. The deposition of the secondary salts over the five pellets in rats was inhibited by the aqueous extract of T. cordifolia. J Res Indian Med. 1966;10:113-6.

[23] Pendse VK, Dadhich AP, Mathur PN, Bal MS, Madan BR. Antiinflammatory, immunosuppressive and some related pharmacological actions of the water extract of Neem Giloe (Tinospora cordifolia): A preliminary report. Indian journal of pharmacology. 1977 Jul 1;9(3):221.

[24] Thattet UM, Dahanukar SA. Immunotherapeutic modification of experimental infections by Indian medicinal plants. Phytotherapy Research. 1989;3(2):43-9.

[25] Rege NN, Nazareth HM, Bapat RD, Dahanukar SA. Modulation of immunosuppression in obstructive jaundice by Tinospora cordifolia. The Indian Journal of Medical Research. 1989 Dec;90:478-83. [PubMed]

[26] Manjrekar PN, Jolly CI, Narayanan S. Comparative studies of the immunomodulatory activity of Tinospora cordifolia and Tinospora sinensis. Fitoterapia. 2000 Jun 1;71(3):254-7. [PubMed]

[27] Dikshit V, Damre AS, Kulkarni KR, Gokhale A, Saraf MN. Preliminary screening of imunocin for immunomodulatory activity. Indian Journal of Pharmaceutical Sciences. 2000;62(4):257.

[28] Dahanukar SA, Thatte UM, Pai N, More PB, Karandikar SM. Immunotherapeutic modification by Tinospora cordifolia of abdominal sepsis induced by caecal ligation in rats. Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology. 1988 Jan;7(1):21-3. [PubMed]

[29] Rege NN, Thatte UM, Dahanukar SA. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 1999 Jun;13(4):275-91. [PubMed]

[30] Thattet UM, Dahanukar SA. Immunotherapeutic modification of experimental infections by Indian medicinal plants. Phytotherapy Research. 1989;3(2):43-9.

[31] Thatte U, Chhabria S, Karandikar SM, Dahanukar S. Immunotherapeutic modification of E. coli induced abdominal sepsis and mortality in mice by Indian medicinal plants. Indian drugs. 1987;25(3):95-7.

[32] Anonymous. 1st ed. Part I. Vol. 1. NewDelhi: Department of AYUSH, Ministry of Health and FW. The Ayurvedic Pharmacopoeia of India; 2001;53–4.

[33] Trikamji Acharya VY, Samgraha SY, Jwaradhikara 1. Varanasi: Shri Baidhnath Ayurveda Bhavan; 2006; 4.

[34] Sharma AK, Singh RH. Screening of anti-inflammatory activity of certain indigenous drugs on carrageenin induced hind paw oedema in rats. Bull. Med. Ethnobot. Res. 1980;2:262.

[35] Wesley JJ, Christina AJ, Chidambaranathan N, Livingston R, Ravikumar K. Effect of alcoholic extract of Tinospora Cordifolia on acute and subacute Inflammation. Pharmacologyonline. 2008;3:683-7.

[36] Pendse VK, Dadhich AP, Mathur PN, Bal MS, Madan BR. Antiinflammatory, immunosuppressive and some related pharmacological actions of the water extract of Neem Giloe (Tinospora cordifolia): A preliminary report. Indian journal of pharmacology. 1977 Jul 1;9(3):221-4.

[37] Utpalendu J, Chattopadhyay RN, Badri PS. Preliminary studies on anti-inflammatory activity of Zingiber officinale Rosc., Vitex negundo Linn and Tinospora cordifolia (willid) Miers in albino rats. Indian journal of pharmacology. 1999 May 1;31(3):232-3.

[38] Gulati OD, Pandey DC. Anti-inflammatory activity of Tinospora cordifolia. Rheumatism. 1982;17(2):76-83.

[39] Gulati OD. Clinical trial of Tinospora cordifolia in rheumatoid arthritis. Rheum. 1980;15:143–8.

[40] Thatte U, Chhabria S, Karandikar SM, Dahanukar S. Immunotherapeutic modification of E. coli induced abdominal sepsis and mortality in mice by Indian medicinal plants. Indian drugs. 1987;25(3):95-7.

[41] Patgiri B, Umretia BL, Vaishnav PU, Prajapati PK, Shukla VJ, Ravishankar B. Anti-inflammatory activity of Guduchi Ghana (aqueous extract of Tinospora Cordifolia Miers.). Ayu. 2014 Jan;35(1):108–110. doi: 10.4103/0974-8520.141958 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213960/#ref12

[42] Pendse VK, Dadhich AP, Mathur PN, Bal MS, Madan BR. Antiinflammatory, immunosuppressive and some related pharmacological actions of the water extract of Neem Giloe (Tinospora cordifolia): A preliminary report. Indian journal of pharmacology. 1977 Jul 1;9(3):221.

[43] Kiuchi F, Shibuya M, Sankawa U. Inhibitors of prostaglandin biosynthesis from ginger. Chemical and pharmaceutical bulletin. 1982 Feb 25;30(2):754-7.

[44] Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chemical and Pharmaceutical Bulletin. 1992 Feb 25;40(2):387-91.

[45] Young HY, Luo YL, Cheng HY, Hsieh WC, Liao JC, Peng WH. Analgesic and anti-inflammatory activities of [6]-gingerol. Journal of ethnopharmacology. 2005 Jan 4;96(1-2):207-10.

[46] Haghighi M, Khalvat A, Toliat T, Jallaei SH. Comparing the effects of ginger (Zingiber officinale) extract and ibuprofen on patients with osteoarthritis. Archives of Iranian Medicine. 2005;8(4):267–71.

[47] Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis & Rheumatism. 2001 Nov;44(11):2531-8. DOI: 10.1002/1529-0131(200111)44:11< 2531:: AID-ART 433 >3.0.CO; 2-J).