Effectiveness of composite Ayurveda regimen in a black box design for the management of Rheumatoid arthritis: Protocol of community-based study

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disease that affects joints and can have extra-articular manifestations. The etiology of RA is unknown, and healthcare systems bear a considerable burden due to its increasing prevalence. Ayurveda has taken the foremost place in managing the corresponding disease “Amavata” through a variety of interventions. The study is aimed to generate leads regarding the effectiveness of composite Ayurveda regimens in the management of RA.

Objective: The clinical study is designed to evaluate the effectiveness and tolerability of a composite Ayurveda regimen in RA.

Methods: The study will be an Open-label, Community-based interventional study with a black box design comprising a sample size of 200 participants of age between 18 and 65 years, diagnosed as per ACR Criteria (2010). Treatment will be classified based on major disease presentation patterns and customized based on the presence of associated symptoms. The outcome measures include change in Disease Activity Score (DAS)-28 with ESR and disease-specific biochemical & inflammatory markers, change in the participant's assessment of pain, Disability Index score, frequency of use of conventional analgesic/NSAIDs(Non-steroidal anti-inflammatory drugs). Tolerability will also be assessed through occurrence of adverse events.

Results: The execution of the study has been initiated in April 2023 with the IEC approval followed by CTRI registration on 20th June 2023. The recruitment of participants has been initiated, as of 7th January 2024, 240 participants have been enrolled and 237 are continuing while 3 participants have dropped out due to incompliance.

Conclusions: The present study will help to assess the effectiveness of composite Ayurveda interventions in various patterns of disease presentation and their tolerability in RA. Clinical Trial: The study is registered with the Clinical Trial Registry of India (CTRI/2023/06/054203) on 20th June 2023.

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Abstract

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that affects joints and can have extra-articular manifestations. The aetiology of RA is unknown, and healthcare systems bear a considerable burden due to its increasing prevalence. Ayurveda has taken the foremost place in managing the corresponding disease "*Amavata*" through variety of interventions. The study is aimed to generate leads regarding effectiveness of composite Ayurveda regimens I n the management of RA.

Objectives

The clinical study is designed to evaluate the effectiveness and tolerability of a composite Ayurveda regimen in RA.

Materials and methods

The study will be an Open-label, Community-based interventional study with a black box design comprising a sample size of 200 participants of age between 18 and 65 years, diagnosed as per ACR Criteria (2010) [1]. Treatment will be classified based on major disease presentation patterns and customized based on the presence of associated symptoms. The outcome measures include change in Disease Activity Score (DAS)-28 [2] with ESR and disease-specific biochemical & inflammatory markers, change in the participant's assessment of pain, Disability Index score, frequency of use of conventional analgesic/NSAIDs(Non-steroidal anti-inflammatory drugs). Tolerability will also be assessed through occurrence of adverse events.

Discussion

The present study will help to assess the effectiveness of composite Ayurveda interventions in various patterns of disease presentation and their tolerability in RA.

Key words: Rheumatoid Arthritis, *Amavata*, Ayush SG (Coded Drug), *Rasnasaptak Kashaya*

Trial registration: The study is registered with the Clinical Trial Registry of India (CTRI/2023/06/054203) on 20th June 2023.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can damage joints and also affect extra-articular organs. In 2019, 18 million people worldwide were living with RA. Women accounted for 70% of cases, and over half were above 55 years of age. [3] The articular manifestation of RA includes symptoms such as musculoskeletal pain, swelling, and stiffness of joints. It commonly develops in tiny peripheral joints, is usually symmetric, and progresses to involve proximal joints if left untreated. Over time, joint inflammation can lead to joint destruction, including loss of cartilage and bone erosion. [4]

The symptoms of RA vary in patients; some patients have mild self-limited disease, while many experience joint destruction, severe physical disability, and multiple comorbidities. RA tends to be progressive in nature, involving a worsening of symptoms over time and often begins for many people during the early or middle years of life, thus causing a heavy burden on society in terms of disability, health, and economic costs. The available evidence for pain management in RA involves the use of disease-modifying anti-rheumatic drugs and medications such as NSAIDs which play an important role in its management, but may suppress the immune system and, lead to an increased risk of infections as well other side effects as gastro-intestinal disturbances. [5,6] People from all over the world are also developing an interest in traditional herbal practices. It is reported that 60 to 90% of persons with arthritic conditions use complementary and alternative medicines.

RA resembles to the condition described in Ayurveda as *'Amavata',* where both the *Ama* (an undigested or intermediate product of digestion or metabolism) and *Vata* Dosha become vitiated and locate in the *Sandhi* (joints) leading to pain and inflammation in the joints. The causative factors for the disease include *Viruddha ahaar-vihar* (incompatible diet and erroneous habits), *Mandagni* (weak digestion), a sedentary lifestyle and exercising immediately after meals. [7]

The Ayurvedic drugs selected in this study i.e. Ayush SG (coded drug) [8,9,10], *Rasna Saptak Kashaya* [11] and *Brihat Saindhawadi Taila* [12] are supposed to act effectively in the management of RA on account of the classical texts and research studies conducted previously. *Guduchi Ghana Vati* [13] *(Sanshamani Vati), Dashang Lepa* [14] and *Punarnava mandoor* [15] are effectively used for associated conditions like fever, inflammation (*Shotha*) and anemia respectively.

The present work has been planned with an objective to evaluate the effectiveness of the Composite Ayurveda Regimen in a black box design in the management of RA. The secondary objectives are to evaluate the effect of Ayurveda Regimen on the disease-specific biochemical, inflammatory markers

of RA and assessment of the tolerability of intervention.

Objectives

The primary objective of the study is to evaluate the effectiveness of a composite Ayurveda regimen on the Disease Activity Score in Rheumatoid arthritis.

The secondary objective is to evaluate the effectiveness of a composite Ayurveda regimen on the disease-specific biochemical and inflammatory markers and assessment of the tolerability of Ayurveda Regimen in Rheumatoid arthritis.

Methodology

Study design

It will be an Open-label, non-randomized, community-based interventional study with black-box research design.

Study setting

The study will be conducted in the identified areas predominantly dwelled by the Scheduled Caste (SC) population at 06 research institutes at New Delhi, Patiala, Guwahati, Gwalior, Vijayawada and Chennai under Central Council for Research in Ayurvedic Sciences, New Delhi, Ministry of Ayush.

Inclusion Criteria

Participants aged between 18 and 65 years, diagnosed with RA (as per ACR 2010 criteria), and willing to give written informed consent for participation will be enrolled in the study.

Exclusion Criteria

Participants presenting with complications of RA e.g. deformity of joints/bones, pleura-pericardial disease, participants with extra-articular manifestations of RA and gastrointestinal symptoms, those with joint prosthesis or unable to walk without support or confined to wheelchair, participants with

Hemoglobin <8 gm %, diagnosed with other arthritis like osteoarthritis, gouty arthritis, tuberculous arthritis, Psoriatic arthritis, spondyloarthropathy, active fibromyalgia, juvenile chronic arthritis, ulcerative colitis, or other systemic inflammatory conditions and auto-immune diseases, having blood pressure ≥ 160/100 mmHg, &/or HbA1C >8 %, on medication with corticosteroids, antidepressants, anticholinergics, etc. Or Ayush interventions/folk medicine or any other drugs that may have an influence on the outcome of the study will be excluded from the study. Participants with diagnosed concurrent neurological, pulmonary, or endocrine disorder, or unstable cardio-vascular disease, with concurrent serious hepatic disorder (defined as Aspartate Amino Transferase (AST) and/or Alanine Amino Transferase (ALT), Total Bilirubin, Alkaline Phosphatase (ALP) > 2 times upper normal limit) or Renal Disorders (defined as S. Creatinine > upper normal limit), Participants with alcohol use disorder (AUD) (CAGE score >2) or any other substance abuse and Pregnant or lactating woman will be excluded from the study.

Study procedure

The participants will be screened from the OPDs/camps/door to door visits in identified area. Before the initiation of the study, the head of the village or local administrative authority and the residents of the area will be informed about the study in detail, in their regional language. Approval from the Institutional Ethics Committee (IEC) of all the concerned institutes has been obtained and the study is registered with CTRI (CTRI/2023/06/054203) on 20th June 2023. The participant will be explained about the study in detail and will be asked to provide consent in writing regarding their participation in the study. Patients with RA will be enrolled based on the defined inclusion and exclusion criteria.

The participants will undergo the following tests – Complete Blood Count (CBC) with Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT), Renal Function Test (RFT) and C - reactive protein (CRP), RA factor (Quantitative), Serum Immunoglobulin (Ig) Levels of IgG, IgM at Baseline and at the end of the treatment (84th Day). HbA1c will be done at Baseline only (Figure 1).

Intervention

Treatment regime will be classified on the basis of major patterns of disease presentation. According to the presence of associated symptoms the treatment for the participants will be customized. All the participants will be prescribed oral medication Ayush SG one gram in tablet form twice a day after meals and *Rasnasaptak Kashaya* 20 ml twice a day (80 ml water will be added in 10 gm of course

powder and will be boiled until remains 20 ml) before meals for 12 weeks. Along with this, *Brihat Saindhavadi tail*a will be given for local application in cases having only articular manifestations (joint pain, stiffness and minimal swelling). Participants with severe pain and swelling (boggy swelling/affusion elicited by fluctuation test), elevated body and/or joint temperature and redness of joint, will be administered *Guduchi Ghana vati (Sanshamani Vati)* orally in the dose of 500 mg twice a day after meals and *Dashanga Lepa* for local application. *Punarnavadi Mandura* will be given orally in the dose of 500 mg twice a day after meals in participants with mild aching, stiffness, fatigue, and anemia.

Withdrawal Criteria

The participant may be withdrawn from the study if the participant is not willing to continue in the study or there is a worsening of symptoms of RA, or if any participant develops any other illness mentioned in the exclusion criteria will be withdrawn from the study. The decision to withdraw a participant from the study would be taken only by the Investigator, who will then have to set out a detailed justification and also indicate the line of further management if needed.

Compliance

During the intervention period, compliance will be evaluated based on the amount of study medication that is consumed. This will be assessed using a compliance assessment form that will be issued to the participants to fill up.

Concomitant Therapy

During the study, the participant shall continue any required concomitant therapy for diabetes mellitus, hypertension or any other disease, which has not been specifically mentioned in the exclusion criteria. The investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care during the intervention period. The name, indication, dose, unit, frequency, start date, and stop date (if applicable) for all interventions (medicine/procedure/therapy) will be recorded on each participant's Case Record Form (CRF).

Outcome measures

Primary Outcome of the study is to observe the change in DAS-28 score (with ESR) from Baseline

to the end of the treatment (84th day).

Secondary Outcome will be measured in terms of change in disease-specific biochemical and inflammatory markers (RA factor, CRP & ESR) and Serum Immunoglobulin Levels (IgG & IgM) from Baseline to 84th day. Change in participants assessment of Pain and Disease Activity will be evaluated through Visual analog scale (VAS) ranged from 0 mm (no pain) to 100 mm (worst pain). Change in Disability Index score (The Indian Health Assessment Questionnaire) and frequency of use of conventional analgesic/NSAIDs medicines will also be assessed and occurrence of adverse events if any, will be recorded within the timeframe of Baseline to 84th day. (Figure 1)

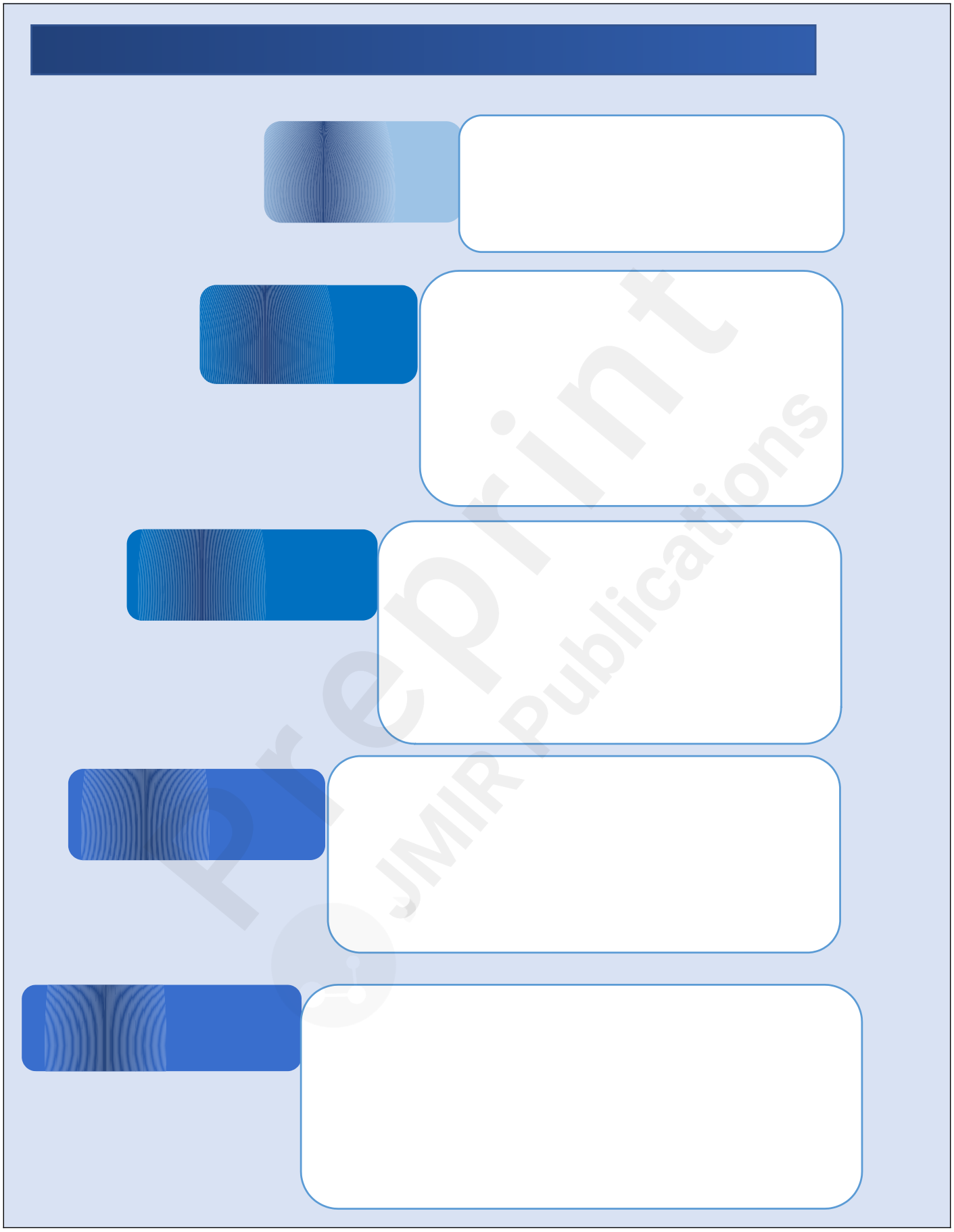

Figure 1: Study Schedule

- ✓ Written Informed consent
- ✓ Clinical Examination

Sample size

Due to the low prevalence of RA (around 0.7% to 1%) [16], it is not feasible to recruit the participants based on the scientific line of sample size theory. Therefore, based on feasibility and the availability of resources, a total of 240 participants will be recruited from 6 institutes (40 participants at each center), within the given timeframe.

Recruitment

The eligible participants will be screened from the outreach OPDS/ camps/ door to door visits conducted in the identified SC dominant area/ village under the selected study sites, following approval from the IEC and registration of the study with CTRI. The participants will be informed about the study in detail (in their regional language) through banners and IEC materials. Written and informed consent will be taken from the participants in their regional language. Recruitment of the participants will be done as per the inclusion and exclusion criteria of the study.

Allocation

Since the study is being conducted in a black box study design and the intervention is classified on the basis of major disease pattern, allocation is not applicable to the present study.

Blinding

The participants will be recruited from the field through door-door survey of clusters with selected population, therefore blinding cannot be achieved.

Data collection methods

Demographic data, clinical history, details of concomitant medications, score of ACR 2010, DAS 28 and other assessment parameters of the participants will be recorded at the Baseline. Contact number of the investigator along with address of the CCRAS institute will be provided to the participants at the time of enrollment. Participants will be instructed to inform about any adverse event if happens during the study period. Follow up of the participants at 28^{th} day ±2, 56^{th} day ±2 and the 84^{th} day ±2. All the data will be recorded in the CRF. During follow-ups, occurrence of any symptom and need for any rescue medication will be recorded. Confidentiality of the data will be maintained. After the completion of the study, the data will be analyzed and published without disclosing the personal identification of the participants.

Besides hard copy of CRF, data will also be filled in e-CRF. All source documentation supporting entries into the CRFs will be maintained and will be kept readily available. To ensure the quality,

the data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. The reason for withdrawal or drop out of participant will be recorded in the CRF.

Data Monitoring

CCRAS Headquarters will monitor the progress of the study to ensure strict adherence to the study protocol and correct documentation of the data. Any problems being faced by the research staff at the participating site will also be addressed.

Deviation from the protocol

Any deviation from the study protocol will be implemented in the study only after approval from the IEC.

Confidentiality

All the information and records of the study participants will be kept confidential and their name and identity will not be disclosed.

Statistical analysis

After collection of the data, it will be verified for its accuracy and limits. The filtered data will be taken for further analysis and interpretation. The categorical data will be described in number and percentage. The continuous data will be described in Mean +/- SD/ Median (Q_1, Q_3) as per the distribution of the continuous variable. In case of comparison of percentage, Paired t-test/ Wilcoxon test will be used to assess the statistical significance between Pre and Post trial. The assessment parameters which have been assigned more than two follow ups will be analyzed by r-ANOVA/ Freidman test, to assess the statistically significant difference among various follow up. During the analysis, the level of significance will be taken at 5%. The SPSS 26.0 software will be used for analysis.

Result

The execution of the study has been initiated in April 2023 with the IEC approval followed by CTRI registration on 20th June 2023. The recruitment of participants has been initiated, as of 7th January 2024, 240 participants have been enrolled and 237 are continuing while 3 participants have dropped

out due to incompliance.

Discussion

Amavata is a type of *Tridoshaja Vyadhi* that is dominated by *Kapha* and *Vata doshas* while RA is characterized by the activation and proliferation of immunomodulated cells like T-cells, macrophages, neutrophils, and plasma cells. The selected Composite Ayurvedic regimen is expected to alleviate symptoms of RA by its *Amapachaka* (detoxifying) activity on *strotas* (functional channels) as well as deranged *Kapha-Vata* dosha and possessing anti-inflammatory, analgesic, and immunomodulatory properties. Different individuals exhibit diverse range of symptoms for the same disease; therefore, multiple set of treatment has been planned according to the clinical presentation of the participants. The overall efficacy of the intervention will be appraised with regard to reduction in the disease activity amongst the participants.

A study has been done on the selected Ayurveda coded drug Ayush-SG, which substantiates the effectiveness of drug in the management of RA. [17]

Rasna saptak Kashaya consists of *Rasna* (Pluchea lanceolata), *Gokshura* (Tribulus terrristeris), *Guduchi* (Tinospora cardifolia), *Punarnava* (Boerrihia diffusa), *Eranda* (Ricinus communis), *Dev Daru* (Cedrus deodara), *Aragvadha* (Cassia fistula) and *Shunthi* (Zingiber officinalis). These plants are well-known for their anti-arthritic, analgesic, and anti-inflammatory properties. *Rasna, Gokshura*, and *Eranda* are among examples. Some of them are recognized for their anti-inflammatory and immunomodulatory properties, such as *Aragvadha* and *Guduchi*. [18] *Rasna* has been found significant in reduction of the inflammation in formalin induced arthritis in albino rats. [19] *Rasna* also possesses flavonoids which are reported to have anti-inflammatory property as scavengers of free radicals and potent inhibitors of lipid peroxidation. [20]

Brihat Saindhavadi Taila has *Tikshna* (pungent), *Ushna* (Hot potency), and *Ruksha* (dryness) properties which effectively reduces discomfort and swelling in joints owing to its *Amapachana* and *Srotosodhana* effects. [21] *Guduchi ghan vati* consists of Tinospora coridifolia, which has *Tikta, Kashaya Rasa, Ushna veerya* and pacifies the deranged *Tridoshas.* [22] It has *Vedana Sthapana* (pain relieving), *Deepana* (enhancing metabolic fire) and *Pachana* (enhancing digestion) qualities. It is well known for its immunomodulatory activity, as demonstrated in a recent animal study which indicates that *Guduchi* is a strong immunogen by itself and enhances the immunogenicity of mucosally-administered antigen in BALB/c mice. [23] Another pre-clinical study conducted on rodents illustrated the anti-inflammatory properties of *Guduchi*. [24] These properties are intended to

improve the condition of debilitated patients suffering from RA.

Dashanga lepa consists of ten indigenous herbs as *Shirisha* (Albizzia lebbeck), *Madhuyashti* (Glycyrrhiza glabra, *Tagara* (Valeriana wallichii), *Raktachandanam* (Pterocarpus santalinus), *Ela* (Eletteria cardamomun), *Jatamansi* (Nordostachys jatamansi), *Haridra* (Curcuma longa), *Daruharidra* (Berberis aristata), *Kushta* (Saussuea lappa) and *Hrivera* (Pavonia odorata). All these synthesize secondary metabolites which possess analgesic and anti-inflammatory properties [25], therefore local application of *Dashang lepa* will alleviate the pain and inflammation of joints in RA patients.

The Drugs present in *Punarnava Mandura* like *Amalaki* (Phylanthus embelica Linn.), *Danti* (Baliospermum momtanum Muell. Arg.), *Pippali* (Piper longum Linn.), *Punarnava*, *Kushtha* (Sausurea lappa) and *Daruharidra* (Berberis aristate DC) are referred to possess immunomodulatory and antioxidant properties, as documented. In addition, *Pippali* is said to be a bioavailability enhancer of the drug, which further helps in the easy assimilation of the drug components. [26] It is also said to have, *Deepana*, *Pachana* properties due to which it acts on *Srotas* and Agni (digestive factors) by enhancing digestive capacity. *Haridra*, *Amalaki*, *Pippali*, *Punarnava*, and *Trivrut* (Operculina terpethum Linn.) present in *Punarnava mandoor* are *Pandughna* (Anemia pacifying) in nature, and increases oxygen-carrying capacity of RBCs may facilitate the heart in its functions. The ferric and ferrous fractions of *Mandura* provide a sufficient amount of iron, which is needed for normal erythropoiesis. [27]

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Conflicts of interest

There is no conflict of interest.

Abbreviations

ACR: American College of Rheumatology
CCRAS: Central Council for Research in Ayurvedic Sciences
CRF: Case record form
CRP: C - reactive protein
CTRI: Clinical Trials Registry- India
DAS: Disease Activity Score
ESR: Erythrocyte sedimentation rate
IEC: Institutional Ethics Committee
NSAIDs: Non-steroidal anti-inflammatory drugs

RA: Rheumatoid arthritis

SC: Scheduled Caste

VAS: Visual analog scale

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