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SYSTEMATIC REVIEW OF PHYTOCONSTITUENTS USED IN RHEUMATOID ARTHRITIS IN RODENT MODELS

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ABSTRACT

Purpose: The objective of this systematic review is to summarize the research information regarding the usage of phytoconstituents in the treatment of rheumatoid arthritis disease.

Method: The research information is collected from online electronic databases like Scopus, PubMed, Science Direct, DOAJ, and J gate using search terms like rheumatoid arthritis OR inflammatory arthritis OR rheumatism OR arthritis OR rheumatic OR polyarthritis. The search strategy has been set considering full-text articles in the English language using rodent models in their study. The review protocol is registered on PROSPERO, and approved on July 12, 2023 (registration no: CRD42023424094).

Result: From the search results 23 articles met the inclusion criteria for the review. These articles were analyzed for the rodent species and strain used, phytoconstituents which improved the paw volume, paw edema and reduction of oxidative stress, amelioration of inflammatory cytokines, and joint swelling.

Discussion: The efficacy of phytoconstituents in ameliorating oxidative stress, paw volume, joint swelling, paw edema, and inflammatory cytokines in various models of experimental rheumatoid arthritis disease is manifested compositely in 23 studies.

Keywords: rheumatoid arthritis; phytoconstituents, rodent models, inflammatory arthritis

INTRODUCTION:

Rheumatoid arthritis is a chronic inflammatory condition characterized by extra-articular involvement, joint pain, bone degradation, and inflammation in the joints. It is a systemic autoimmune disease that starts at the peripheral joint and progressively involves the proximal joint [1]. The prevalence of Rheumatoid Arthritis is 3-5 times higher in females [2]. The risk of Rheumatoid Arthritis increases with age, between 65 to 85 years of age [3]. Rheumatoid Arthritis caused due to many factors such as genetic factors, environmental factors, and immunological factors. Cigarette smoking is a significant risk factor for the development of Rheumatoid Arthritis [4].

The pathophysiology of Rheumatoid Arthritis involves the presence of autoantibodies such as Rheumatoid Factor and anti-citrullinated peptide antibodies. Rheumatoid Factor is an IgM antibody against IgG. The formation of antigen-antibody complexes in the joint serves as the initiator for chronic inflammatory responses that lead to the development of Rheumatoid Arthritis. Anti-CCP antibodies are highly specific for rheumatoid arthritis, and those with other diseases or no rheumatoid arthritis are rarely discovered to have them [5]. Proteins and peptides' arginine residues undergo the post-

translational modification of citrulline. A polymorphism in the PAD4 gene may lead to increased citrullination [6]. The inflammation is mainly focused on synovium [7]. The HLA-DR gene, particularly its HLA-DR4 subtype, remains the main genetic risk factor for rheumatoid arthritis, which causes the activation of T cells. It is a distinct genetic marker located in a specific gene.

The current treatment of Rheumatoid Arthritis includes NSAIDS, DMARD, Glucocorticoids, and biologic drugs [8]. Disease-modifying anti-rheumatic drugs such as Methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. The release of mediators such as cytokines, granulocyte monocyte colony-stimulating factors, and interferons occurs during chronic inflammation. These mediators are in charge of the pain, cartilage and bone degeneration, and severe impairment that they cause [9]. In recent times therapies based on natural sources are improving due to their fewer side effects.

AIM AND OBJECTIVE OF THE STUDY:

Our study aimed to assess the possible role of phytoconstituents in the management of rheumatoid arthritis, or RA.

DATA SOURCES AND SEARCH:

An exhaustive search of articles from scholarly journals looking into the impact of phytoconstituents in rheumatoid arthritis disease through online electronic databases like Scopus, PubMed, Science Direct, DOAJ, and J gate were collected. Search terms like rheumatoid arthritis OR inflammatory arthritis OR rheumatism OR arthritis OR rheumatic OR polyarthritis AND phytoconstituents were used. The literature search was conducted on 20th March 2023. Using AND, and OR as Boolean operators the articles published in the English language are retrieved from the database from March 2023 to April 2023.

METHODOLOGY: PRISMA, or preferred reporting items for systematic reviews and meta-analyses, was followed in this investigation.

Eligibility criteria:

All research article includes in-vivo experiments in their studies involving parameters like Paw volume, paw diameter, levels of inflammatory cytokines like TNF- α , IL-1 β , oxidative stress, and m-RNA expression by PCR retrieved.

Outcome:

Studies with outcome measurement of paw volume, paw edema, arthritic index score, cytokines levels, histopathological analysis of paw, hematology, and biochemical parameters were included.

Study selection:

An initial search was conducted by one reviewer (RK). The eligible records' titles, abstracts, authors, keywords, volumes, issues, and DOIs were exported in CSV files from databases with relation to Microsoft Excel for further screening of duplicates. After removing duplicates, The articles' eligibility was evaluated by a second reviewer (GK) to reduce the bias in the selection of records. Records that meet the above criteria are taken for further screening.

Data extraction:

All the collected data were fed into an Excel spreadsheet for further reference. The second reviewer confirmed the data significance and persistent consistency of the extracted information from each report.

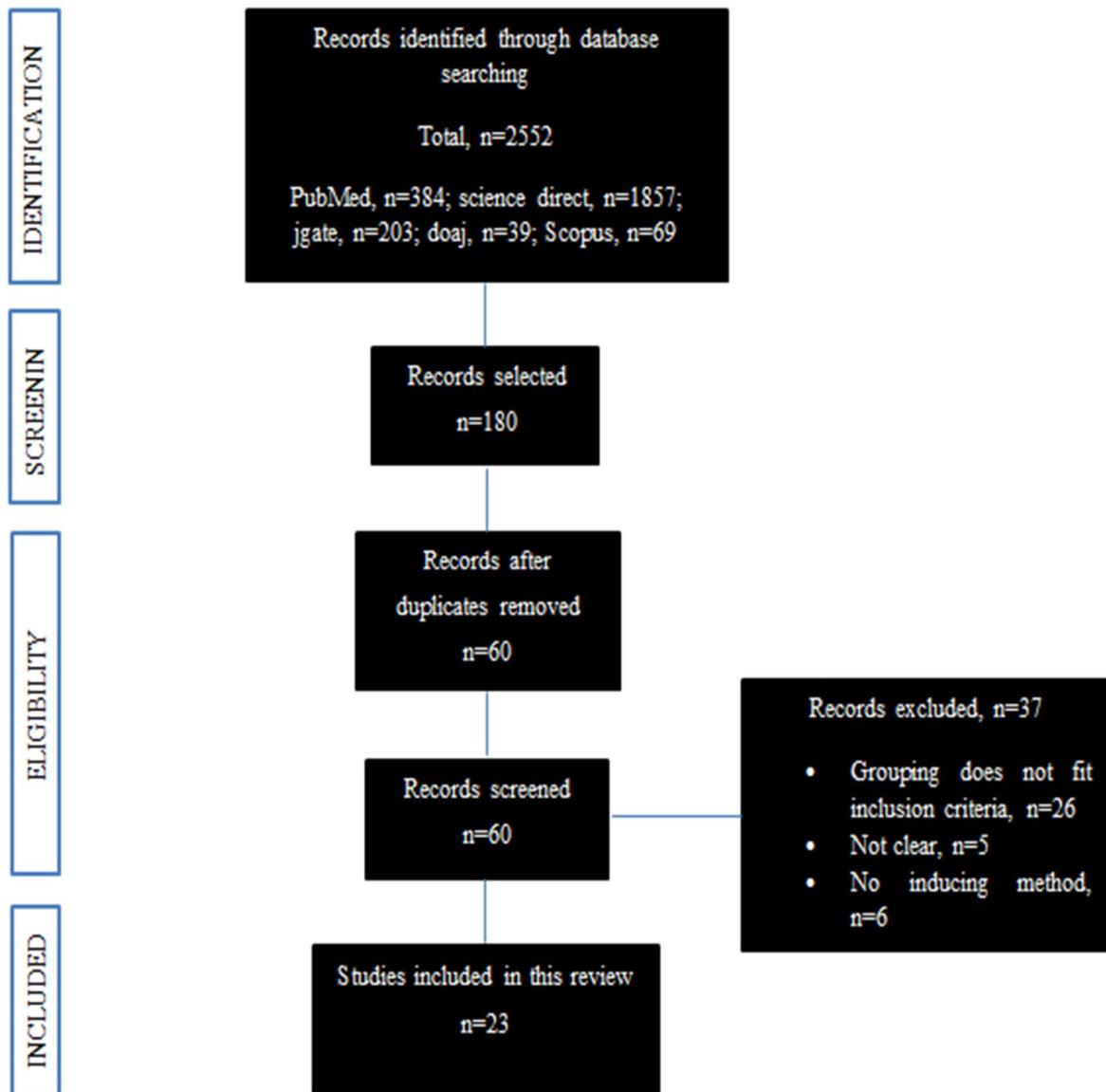


Figure 1: The Prisma flow diagram of the studies in this review

Table 1: Characteristics of 23 reports included in the review

S.NO	AUTHOR YEAR	ANIMAL	GROUPING	INDUCIN G AGENT	DRUG TREATMENT	PARAMETERS CHECKED	OUTCOME
1	Farrukh M, Saleem U, Ahmad B, Chauhdary Z, Alsharif I, Manan M, Qasim M, Alhasani RH, Shah GM, Shah MA 2022	Wistar rats, 150 to 200 g, Male and female.	6 groups, n=5 Control Disease Diclofenac sodium Aq.methanolic plant extract 250mg/kg Aq.methanolic plant extract 500mg/kg Aq.methanolic plant extract 1000mg/kg	150 µL CFA	Aq methanolic plant extract 250,500,1000mg/kg	Paw diameter Arthritic index Histopathology hematological biochemical analysis	Methanolic extract from plants reduced the arthritic index score and paw diameter.
2.	Majid M, Nasir B, Zahra SS, Khan MR, Mirza B, Haq IU 2018	Sd rats, 150-200g, Male	7 groups, n=6 IPT EA IPT M IPR EA IPR M Positive Disease normal	200 µL CFA 11-13 days	Ipomoea batatas 300mg/kg	Measurement of cytokines serum levels antioxidant enzymes Biochemical parameter Hematological studies	Batatas reduces oxidative damage and both acute and chronic inflammation inhibits inflammatory edema.
3.	Tang Y, Xie D, Gong W, Wu H, Qiang Y 2021	Wistar rats, Adult female, 150-200g	6 groups 1 and 2 normally received 10mg/kg DMSO 3 leflunomide 10mg/kg in DMSO 4 to 6 QTN IN DMSO	0.1 ML FCA 32 DAYS	QTN	Oxidative stress Synovial pro-inflammatory cytokines protein expression of cox-2, nf-kβ, p2x7 histopathology of the tibiotarsal joint.	Madhuca indica manages inflammatory disorders due to its inhibitory potential against histamine, serotonin, and cox-2. QTN ameliorates elevated inflammatory mediators and oxidative stress.
4.	Niazi SG, Uttra AM, Qaiser MN, Ahsan H 2017	Sd rats, either sex, 150-200g	5 groups 1-formalaldehyde+distilled water 2- formalaldehyde+aspirin 3,4,5- formalaldehyde+AMECR	Formalde hyde 0.1ml	AMECR 200,400,600mg/kg for 10 days	Bovine serum albumin Protein denaturation inhibition	Plant extract protects bovine serum albumin and egg albumin denaturation.
5.	Petchi RR, Vijaya C, Parasuraman S 2013	Sd rats, Female, 180-200g	5 groups Vehicle control Arthritic control T.procumbens 250mg/kg T.procumbens 500mg/kg Indomethacin 10mg/kg	FCA 0.1ml 20 days	Ethanollic extract of T.procumbens at 250 and 500mg/kg	Biochemical parameter Radiographic analysis	T.procumbens indicated the presence of alkaloids, tannins, flavonoids, and saponins.
6.	Rajendran R, Krishnakumar E 2010	Wistar albino rats, Female, 150-200g	3 groups Control Indomethacin Premna serratifolia	FCA 0.05ML 21 DAYS	Ethanollic extract of premna serratifolia 300mg/kg	Paw diameter Body weight Blood withdrawn	Ethanollic extract at 300mg/kg inhibited paw edema.
7.	Ruknuddin G, Patgiri BJ, Prajapati PK, Ashok BK, Ravishankar B.	Charles foster albino rats, either sex, 200g	4 groups Control Arthritic control Test drug Dexamathasone 45mg/kg	0.1ml FCA	Dashanga ganga 2000mg/kg	Paw diameter Blood and biochemical parameter Body weight	Attenuation of blood urea level in dashanga ganga.

9.	Manoharan AL, Jagadeesan G, Nataraj G, Muniyandi K, Guruswami G, Arunachalam K, Thangaraj P.2023	rats	5groups vehicle control negative control positive control TPEA EXTRACT 250mg/kg 500mg/kg TPEA extract	0.1ml CFA 21 days	TPEA 250,500mg/kg	Body weight Paw volume Biochemical Hematological C-reactive protein Rheumatoid factor	TPEA extract showed higher anti-arthritis (32.4%)inhibition.
10	Dhakad PK, Sharma PK, Kumar S 2018	Wistar rat, female, 150-200g	6 groups n=6 normal control FCA-induced arthritic control diclofenac sodium 5mg/kg C.decidua 100mg/kg C.decidua 200mg/kg per se group 200mg/kg	0.1ml FCA	Hydroalcoholic extract of C.decidua 100mg/kg and 200mg/kg 28 days	Body weight Paw volume Hematological parameter Histopathological analysis	C.decidua extract reduced the hematological change, paw volume, and body weight.
11	Padhi K,Somani R,Pradhan D 2018	BALB/C mice, 25-30g 10 weeks old	4 groups n=6 Control Trans cinnamaldehyde 100mg/kg CFA 0.1ml Methotrexate 0.75mg/kg	0.1ml CFA	Trans-cinnamaldehyde 100mg/kg	RF in serum Histopathology Immunohistory Elisa measurement	TCA decreases suppresses the development of arthritis and the inflammatory reactions brought on by TNF/IL-1, /IL-6/IL-23 signals.
12	M KC, Y PS, S YP, Jadhav, B MV 2014	Wistar rats, Male, 150-200g	5 groups n=6 Normal control CFA0.1ml Diclofenac 10mg/kg HECE 200mg/kg HECE 400mg/kg	0.1ml CFA 21day	HECE 200 and 400mg/kg	Paw volume, estimation of serum parameter	HECE 400mg/kg decrease in paw volume, HECE 200mg/kg decrease in paw diameter.
13	Suyog G,Deepti B,Beautikumari S,Ankita P 2014	Wistar rats male 130-150g	6 groups n=6 Normal control FCA Indomethacin 2mg/kg PGTF 50mg/kg PGTF100mg/kg PGTF200mg/kg	0.1ml FCA	PGTF-50,100,200 mg	Body weight Paw swelling Arthritic index	Reduction in paw edema, arthritic index, urinary hydroxyproline.
14	V DN, N PA, A SS, a V P2013	Wistar rats,male,150-250g	6 groups n=6 Control CFA 0.1ml Diclofenac AEAM 100mg/kg AEAM 200mg/kg AEAM 400mg/kg	0.1ml CFA	AEAM 100,200,400mg/kg	Paw edema Paw diameter Body weight Serum parameter	AEAM showed a reduction in paw edema.
15	Sutharsingh R,Kavimani S,Jayakar B,Uvarani M,Thangatirupathi A 2011	Swiss albino rat, 200g, Either sex	4 group n=6 Control 200mg/kg Chloroform 200mg/kg Ethanol extract Prednisolone 10mg/kg	0.05ml CFA 21 DAYS7	Naravelia zeylanica extract 10mg/kg	Paw edema	Reduction in the volume of the paws of rats given ethanol and chloroform extract.
16	Shokry AA,El-Shiekh RA,Kamel G,Bakr AF,Sabry D,Ramadan A2022	Wistar rats, Male, 150-170g	7 groups n=10 Control negative Control positive CFA Ibuprofen	0.1ml CFA	TIE 100,200mg/kg	Paw swelling Body weight Histopathology	TIE-E 200mg/kg covered the edema of the paws, serum immunological indicator, and inflammatory

			TIE-E100MG/KG TIE-E 200MG/KG SAP-F 100MG/KG FLAV-F 100mg/kg			Inflammatory parameter	cytokines with an increase in anti-inflammatory cytokines.
17	Mahdi HJ,Khan NA,Asmawi MZ,Mahmud R,A/L Murugaiyah V 2018	Sd rats, Male, 150-200g, 8-10 weeks old	5 groups, n=6 Control CFA Indomethacin 2.5mg/kg 500mg/kg moringa extract 250mg/kg moringa extract	0.1ml FCA	Moringa extract 250,500mg/kg	Arthritic index X-ray radiographic analysis Paw edema	Moringa extract is effective in preventing the development of arthritis disease severity.
18	Choudhary M, Kumar V, Gupta PK, Singh S 2014	Sd rats, Either sex, 200-300g	5 group Control FCA EABP 125MG/KG EABP 250MG/KG Diclofenac sodium 4mg/kg	0.1ml FCA	EABP 125,250 mg/kg	Arthritic score Paw volume Hematology Histopathology	The extract at 250mg/kg showed more potent paw edema inhibition.
19	Das C,Bose A,Das D 2021	Wistar rats, 150-175 g, Either sex	8 groups, n=6 Control CFA Indomethacin 1mg/kg IBF M1 2.31ML/KG IBF M2 2.31ML/KG IBF M3 2.31ML/KG IBF M4 2.31ML/KG	0.1mlCFA	Balarista formulation 2.31ml/kg	Arthritic index Paw diameter Body weight Hematology Anti-oxidant activity Biochemical estimation	Oxidative stress is counteracted by the formulation.
20	Syed Zameer Ahmed K, Ahmed SS, Thangakumar A, Krishnaveni R 2019	Female rats, 160-180g	5 grp Control Arthritic control PT 100mg/kg PT 200MG/KG Indomethacin 10mg/kg	0.1ml CFA	PT 100mg/kg,200mg/kg	Paw swelling Arthritic score Radiographic analysis Blood analysis	PT reduces complications associated with arthritis.
21	Swathi KP,Jayaram S,Sugumar D,Rymbai E 2021	Wistar rats, Female, 160-180g	4grp n=6 Control CFA 0.1ml CFA+ diclofenac 10mg/kg CFA+EECT 200mg/kg	0.1ml CFA	EECT 200mg/kg	Catalase, arthritic activity Paw erythema Paw swelling Histology Radiology	EECT 200,400mg/kg showed a decrease in paw diameter.
22	Gokhale JP,Mahajan HS,Surana SJ	Wistar rats, Male, 140+15g	4 grp n=6 CFA control QCT QCT-NE gel Diclofenac	0.1ml CFA	QCT gel	Paw volume Arthritic index Joint stiffness Hematological parameter	The gel showed inhibition of paw edema over 24hr.
23	Patel MG,Pundarikakshudu K 2016	Wistar rats, Male, 200-250g	6groups n=6 Control Disease Indomethacin 10mg/kg VGE 135mg/kg VGE 270mg/kg 540mg/kg	0.1ml CFA	VGE	Paw volume Body weight Blood analysis	VGE produced significant inhibition of joint swelling in CFA-induced arthritis.

RESULTS:

Evaluation of the reports' quality: Cohen's kappa statistics measure the probability and agreement of variance between the reviewers. When the inter-rater reliability of SH and CV was tested using the kappa statistic, the results showed a score of $\kappa=0.643$ ($SE=0.093$; 95% CI: from 0.461 to 0.826; weighed $\kappa=0.643$), indicating substantial agreement.

Selection of reports: 2552 entries were found in the initial search across five databases, of which 384 were from PubMed, 1857 from Science Direct, 203 from J Gate, 39 from DOAJ, and 69 from Scopus. After the removal of duplicates, 60 records were screened and 23 were selected which met the inclusion criteria. Others were rejected for the following reasons; 26 articles did not use the control group in their study, 5 articles were rejected since their grouping is not clearly explained and 5 articles did not use the inducing method. The PRISMA flow chart of the above selection and screening process is depicted in **Figure 1**.

Experimental animals: The study outcome of all 23 articles that met our inclusion criteria is obtained in Table 1. Five out of twenty-five investigations used Sprague Dawley rats. Eleven studies used Wistar rats. BALB/C mice were used in one study. Swiss albino rats

were used in one study. Wistar albino rats were used in one study. Two studies did not mention any species in their paper. Charles foster albino rats were used in one study. Eight studies preferred male animals and eight studies preferred female animals. eight studies failed to mention the sex of the animal. The vast majority of studies induced experimental rheumatoid arthritis by subcutaneous or sub-plantar injection of Freund's complete adjuvant (0.1ML)(n=21). Supplanter injection of formaldehyde in two studies.

Outcome measures: All the reports cited in this review measured various biochemical parameters. Using a digital vernier caliper, the most typical metric in this measurement was paw diameter in 5 studies. ELISA analysis was performed for quantitative analysis of IL-6, TNF, HSP-70, and BC12 in 4 studies. By using qRT-PCR, pro-inflammatory and anti-inflammatory mediators, as well as metabolic enzymes, were quantitatively assessed in blood samples from experimental rats. in 2 studies. Haematocytometer was used to assess blood parameters including platelet count, erythrocyte sedimentation rate (ESR), white and red blood cells, hemoglobin (Hb) in 11 studies. Biochemical parameters such as rheumatoid factor (RF), aspartate transaminase (AST), alanine transaminase, urea, and alkaline phosphatase in 9 studies. In

the Arthritic index, the intensity of disease was determined in the hind paw and that can be scored from 0 to 4 was performed in 7 studies. Radiographic analysis was performed in 4 studies. Histological examination was done in 7 studies. The assessment of oxidative stress indicators using appropriate kits, such as CAT and SOD, and MDA in 3 studies. The protein expression in 2 studies. The body weight was measured in 9 studies. The volume of paw edema was measured by plethysmometer in 9 studies.

DISCUSSION:

This review's objective was to assess the impact of phytoconstituents from the perspective of recovering arthritic index, inflammatory mediators, and oxidative stress caused by rheumatoid arthritis disease and to communicate the applicability of existing literature as a support for future research. Although there were no date limits applied to any databases, the papers that were gathered were all published after 2010, indicating that the effectiveness of phytoconstituents in treating rheumatoid arthritis disease has been studied over the previous ten years.

Rheumatoid arthritis is a chronic inflammatory condition characterized by extra-articular involvement, joint pain, bone degradation, and inflammation in the joints. Environmental Factors Linked to a Higher

Risk of RA Development are environmental factors exposure including smoking, silica, asbestos, textile dust, and *p.gingivalis*. Rheumatoid arthritis patients must get both pharmaceutical and non-pharmacological therapy [33]. Recently plant-based treatment serves as a good alternative to synthetic drugs due to their fewer side effects [34]. Plant derivatives containing steroids, immunosuppressive, antioxidants, flavonoids, phenols, and terpenoids have anti-arthritic activity. Among these phytoconstituents with anti-inflammatory activity are effective against Rheumatoid arthritis which potentially target TNF-, IL-1b, IL-6, IL-8, NF-K, COX-2, COX-5, MMP, and IL-1b. This review speculates the effect of phytoconstituents from natural sources such as *sarcococca saligna*, *ipomoea batatas*, *Madhuca indica*, *Cuscuta reflexa*, *Tridax procumbens*, *Premna serratifolia*, *Dashanga Ghana*, *Achyranthes aspera*, *Trevesia palmata*, *Capparis Decidua*, *Cinnamaldehyde*, *Colocasia Esculenta*, *Punica Granatum*, *Aegle Marmelos*, *Naravelia Zeylenica* in treating rheumatoid arthritis disease. The 23-research article included in this review used sources of phytoconstituents to treat experimental rheumatoid arthritis induced by different inducing agents.

Increased ESR in the present study indicates the anemic conditions which is a common

diagnostic feature in patients with chronic arthritis. Biochemical parameters such as C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase, urea, alkaline phosphatase, and rheumatoid factor (RF). ELISA analysis was performed for quantitative analysis of IL-6, TNF-, HSP-70, BC12. By using qRT-PCR, pro-inflammatory and anti-inflammatory mediators, as well as metabolic enzymes, were quantitatively assessed in blood samples from experimental rats. Hematocytometer was employed to assess blood components such hemoglobin (Hb), white and red blood cells, erythrocyte sedimentation rate (ESR), and platelet count. Clinical trials of the above-mentioned interventions should be focused on improving the treatment for the disease.

CONCLUSION:

This systematic review highlights the potential of phytoconstituents as a therapeutic intervention in rheumatoid arthritis disease. The studies reported in this review insinuate the target of phytoconstituents in rheumatoid arthritis disease and their mechanism of action against oxidative stress, inflammatory mediators, paw diameter, arthritic index, and serum concentration. The evidence from the reported studies proves that phytoconstituents can

ameliorate the negative effects of rheumatoid arthritis disease.

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PROTOCOL REGISTRATION: The International Prospective Register of Systematic Reviews (PROSPERO) received a prospective registration of this systematic review and was approved on July 12, 2023 (registration no: CRD42023424094).

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT:

Razya Sulthana Beevi, K: Data curation, Formal analysis, Conceptualization, Writing – original draft, Writing – review & editing. **J. Gowri K:** Data curation, Conceptualization, Formal analysis, Writing – review & editing. **Chitra, V:** Software, Validation, Formal analysis, Writing – review & editing. **Chitra, V:** Formal analysis, Validation.

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CONFLICT OF INTEREST: There are no declared conflicts of interest by the authors.

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