IJPSR (2022), Volume 13, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 June 2021; received in revised form, 03 August 2021; accepted, 05 August 2021; published 01 April 2022

# A REVIEW ON HERBAL DRUGS WITH POTENTIAL ANTI-ARTHRITIC ACTIVITY

Shanaz Banu [1] and Leemol Varghese [* 2, 3]

Department of Pharmacognosy [1], Dayananda Sagar University [2], Bengaluru - 560078, Karnataka, India.
Sarojini Naidu Vanita Pharmacy College [3], Hyderabad - 500017, Telangana, India.

**Keywords:**

Rheumatoid arthritis, Phytoconstituents, Early Diagnosis, Drug treatment

**Correspondence to Author:**
**Mr. Leemol Varghese**

Assistant Professor,
Sarojini Naidu Vanita Pharmacy College, Hyderabad - 500017, Telangana, India.

**E-mail:** leemolvarghese1@gmail.com

**ABSTRACT:** Rheumatoid arthritis (RA) is a general inflammatory disorder touching about 1.3% of the grown-up census of the world. Over the last two decades, a significant development has been done in the thoughtfulness of RA pathophysiology, best outcomes, and successful treatment strategy, and the credit of the significance of diagnostic agents and treating RA near the beginning. Earlier than novel treatments were obtained, RA caused notable incapability and deaths. At present, it is customary that principal diagnostic agents and therapy are significant and helpful. Development in the treatment of RA made it likely to manipulate signs in inflammatory arthritis. The early hour diagnosis and treatment of RA can prevent or reduce the progression of joint erosion to about 90% of patients; by this means irreversible disability can be prevented. In advance and more effective treatment significantly improves the prognosis of RA. The advancement of novel instruments to assess disease activity and recognize remission has brought about innovative treatment strategies to inhibit RA ahead of joint damage forever. The pharmacological therapy consists of the nonsteroidal anti-inflammatory drug (NSAIDs), glucocorticoids (GC); disease-modifying antirheumatic drugs (DMARDs), biological drugs is of two types: 1) Monoclonal antibodies, 2) bisphosphonate agents. The price of a few treatments is considerable, but their use has come down with the advancement of biosimilars. A target-treatment strategy aims to decrease disease activity by around 50% in three months and achieve a reduction of disease succession in six months, with continuous therapy if needed, which can prevent RA-related disability. There is a restoration of attention in plant products because of the present belief that green medicine is safer and more trustworthy than expensive synthetic drugs. The outlook is towards the synchronized multidimensional research intended to correlate botanical and phytochemical activities to exact anti-arthritic activity is achieved.

**INTRODUCTION:** RA is an inflammatory rheumatic disorder in which moving articular and extra-articular parts cause ache, disability, and death [1, 4]. It causes chronic inflammation, which is a systemic autoimmune disorder, at first disturbing to small bones and then the larger ones, eventually to skin, eyes, heart, kidneys, and lungs.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(4).1479-87

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(4).1479-87

Frequently, joints and cartilage of bones are damaged; tendons and ligaments are destroyed [5, 7]. Constant inflammation causes erosion of joints and practical injury in the huge bulk of patients [8, 11].

RA results in severe ache, bulge, rigidity, and lack of activity in bones. It damages any bone still commonly affects bones of the wrist and fingers. Further, women are affected than men by RA. It usually begins in middle age and is very general in elderly people [12, 15]. Natural products from plants play an extraordinary function in treating and prevent many pathological conditions from olden times. Research examined by World Health Organization (WHO) has concluded that

approximately 80% of world's population depends on conventional therapy [16, 21]. In the USA, about 121 therapeutic agents are prescribed, 90 of them are from the natural agents chiefly from plants in a straight or indirect way. Herbal remedy will be a source to alleviate signs of RA and handle the problems linked with current therapy of allopathic agents [27].

**Signs:** RA signs depend on the extent of membrane inflammatory reaction. During membrane inflammation, disease is vigorous. AS membrane inflammatory reaction suppresses, the disorder becomes dormant, as called remission. During the active state, RA symptoms appear: exhaustion, lack of energy, decreased craving for food, low fever, muscle and ache, flush, bump, softness, deformity, nodules, rigidity, and lack of movement reduced bone activity [22, 23].

As reported by the Centres for Disease Control and Prevention (CDC), the signs typically distress equivalent bones on either side of body [24, 28].

Rarely, RA damages the joint, resulting in the contraction of voice cords to change the tone of voice. This causes horse voice [29, 31]. Signs are usually on and off. Through remission, symptoms vanish, or can be mild. Conversely, through a flare, symptoms will be severe [32].

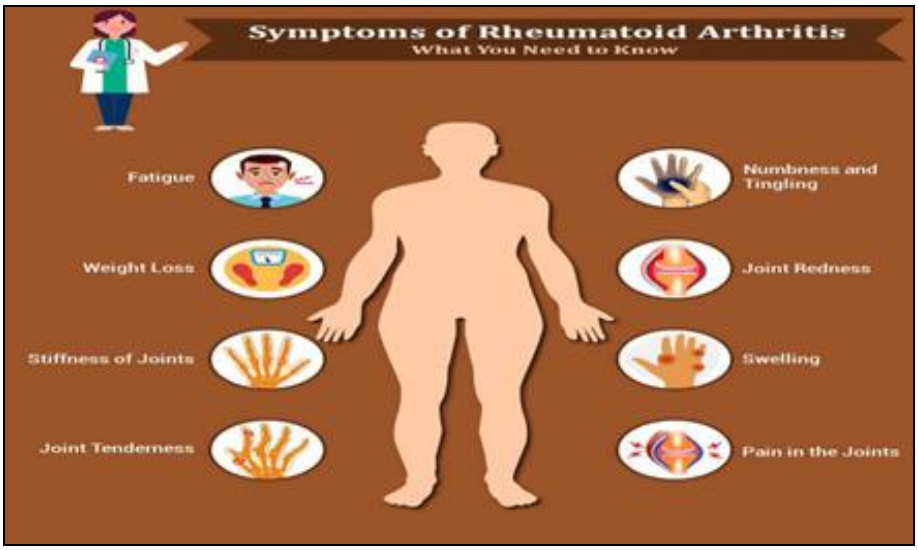


**FIG. 1: SIGNS OF RA**

**Pathophysiology:** The core reason of RA is unidentified. Although viruses, bacteria, and fungi have extensively been assumed, but not been proved. It is thought that the propensity to grow RA may be hereditary [33, 34]. RA is classified as an autoimmune disease, which occurs due to the over-activity of the immune structure by offending the body's own cells and tissues. In people with RA, the immune system stimulates unusual inflammation in the membrane that covers joints *i.e.*, the synovial membrane. Inflammation of synovium; causes ache, swelling, and stiffness of joints. In harsh situations, inflammatory reactions damage the bone, joints and surrounding tissues within the joints, resulting in bigger damages [35]. Immune cells, called lymphocytes, are stimulated, and chemical messengers (cytokines, such as tumor necrosis factor/TNF, interleukin-1/IL-1, and interleukin-6/IL-6) are produced in the inflamed regions [36, 39]. Synovial fibroblasts are major players in RA. They motivate a pro-inflammatory situation in the synovial membrane, cooperate with the immune system, and control the differentiation of monocytes to osteoclasts [39, 42].

Major genetic agents of RA are variations in Human Leukocyte Antigen (HLA), particularly the HLA-DRB1 gene. The amino acids synthesized by HLA assist the immunity to differentiate its own amino acids apart from foreign ones of viruses and bacteria [43, 48].

Environmental agents also appear to take a prime role in causing RA. Smoking tobacco, contact with silica, and long-term periodontal disorders raise the threat of budding RA. Studies regarding gut organisms that can stimulate the beginning of RA in hereditarily vulnerable candidates [49, 50].

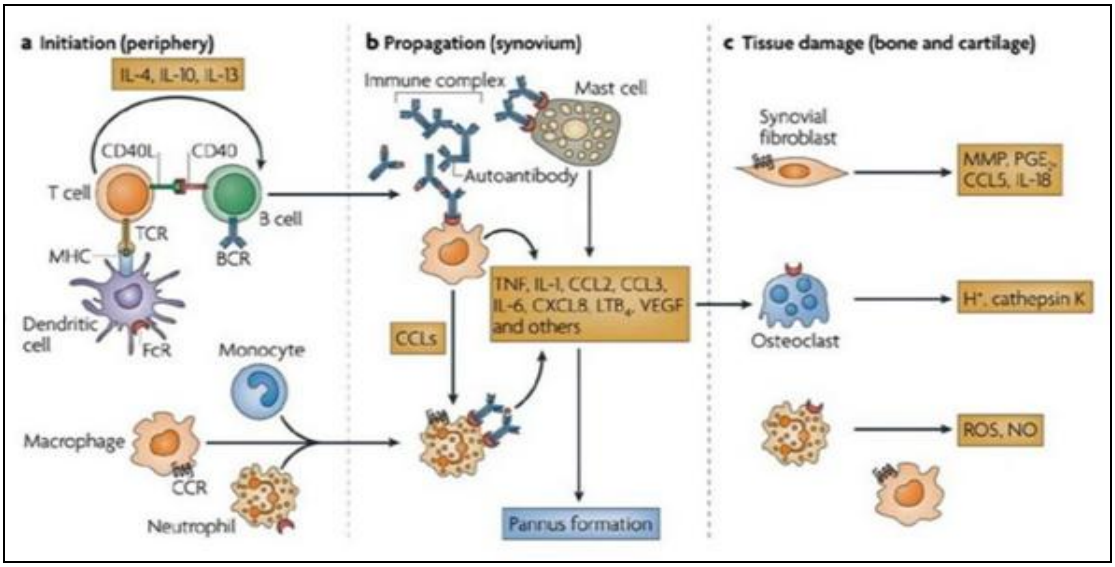


**FIG. 2: RHEUMATOID ARTHRITIS PATHOPHYSILOGY** CD40=cluster of differentiation 40, co-stimulatory protein present of antigen presenting cell(APC); CD40L= cluster of differentiation 41-LIgant present of th cell, bind to CD40 to activate APC; TCR=T cell receptor; BCR=B cell receptor MHC= major histocompactibility complex= surface receptor, with its ligand activate TCR; FCR receptor = protein receptor present on immune cells, CCR=c-c-motif receptor= beta chemokine receptor; CCL5= chemokine (c-c-motif) ligant-5=RANTES= its chemo tactic for neotrophils; CCL2= chemokine (c-c-motif) ligant-2= MCP; CCL3= chemokine (c-c-motif) ligant-3MIP-1; CXCL8=IL8; LTB=TNF-C= induce inflammatory response; VEGF= vascular endothelial growth factor, Pannus= abnormal fibrovasculor tissue lies over joint surface; MM matrix metalloproteinase PGE= prostaglandin E; IL-IB= interleukin -1 beta; cathepsin k= enzyme regulating bone remodelling; ROS= reactive oxygen species; NO= nitric oxide; IL-4= interleukin-4; IL-10 = interleukin-10 IL-13= interleukin-13; T cell = T lymphocyte; B cell = B lymphocyte; TNF= tumor necrosis factored; IL-1= interleukin-1

**Risk Factors and Complications:** CDC reported that patients with an elevated threat of attacking RA can comprise individuals of age 60 years or above, female, overweight, smoking [50, 55].

**Diagnosis:** The diagnosis depends on the clinical presentation. The existence of rheumatoid factor and citrulline antibody (Abs). The occurrence of nodules and X-ray changes [55].

**Antinuclear Antibody (ANA) Test:** Presence of antinuclear Abs in blood. The test detects antinuclear Abs in blood and confirms autoimmune disease. On taking the blood samples from veins of arms, positive result on an ANA test explains that antinuclear antibodies were confirmed in blood. Individuals may expect a positive result if:

- Person has SLE (lupus).
- Person has an autoimmune disorder.
- Person has a viral infection.

**Cyclic Citrullinated Peptide Antibody:** This test helps confirm RA and differentiate it from other arthritis and estimate the prognosis of RA patients. Cyclic citrullinated peptide antibodies are those released by the immune systems which are focussed against cyclic citrullinated peptides (CCP). This test identifies and calculates anti-CCP antibodies in the blood. Citrulline is formed in the body due to the metabolism of amino acid arginine. Though, in joints with RA, this translation happens at a higher rate. Citrulline modifies protein configuration and stimulates an immune response, forming autoantibodies in opposition to joint proteins. The CCP antibody test confirms the diagnosis of RA and is used in recognizing patients with the quickly erosive type of disease.

**Erythrocyte Sedimentation Rate (ESR):** ESR is a test that calculates how rapidly RBC settles down. In general, red cells settle comparatively slowly. A faster rate confirms inflammation in the body. Higher ESR shows inflammatory disorders [55, 59].

**Stages Of Rheumatoid Arthritis"** The stages of RA by the condition of cartilage, ligament, and joints are as follows.

**Stage I:** early RA: Negative effect on X-ray, whereas symptoms of joint thinning may be present.

**Stage II:** moderate progressive: X-ray confirmation of joint thinning surrounding a bone with or devoid of little joint erosion.

- little cartilage destruction is probable
- Joint movement is restricted; the absence of bone deformities are seen
- Atrophy of surrounding soft tissue
- Damage of muscle adjacent to joints.

**Stage III:** severe progression:

- X-ray examination of joints shows erosion
- Joints deformities with reversible stiffness joints
- Widespread soft tissue atrophy

**Stage IV: terminal progression:**

- X-ray observation of joint damage and osteoporosis surrounding the joints.
- Joint deformities with irreversible stiffness of the joints (ankylosis)
- Widespread soft tissue atrophy and abnormalities

**Physicians Categorize The Position RA Patients as Follows:**

- Capable of carrying out normal functions of everyday
- Capable of carrying out common self-care except in working outdoor like playing sports.
- Capable of executing normal self-care but restricted in other jobs
- Incomplete capability to execute normal self-care and activities [60, 63.]

**Treatment:**

**Non-Pharmacological Treatment:**

**Rest:** During a flare, the patient should rest. Swollen and acheful bones make signs worse.

**Exercise:** Upon remission, signs are gentle; patients must often exercise to improve health and reinforce the soft tissues surrounding the bones. The finest workout is that which does no tension on the bones, like swimming.

**Diet:** Subsequently, healthy food with lots of fruits and vegetables will improve the patient, allow feeling better, and maintaining a healthy weight [64, 65].

**Pharmacological Treatment:**

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):** Chronic administration and high concentrations result in adverse effects like gastric upset, elevated BP, kidney damage, and liver injuries [66].

**Corticosteroids:** They intend to decrease aches and inflammatory responses and can slow down bone injuries, although they may not heal RA. Corticosteroids are very useful in acute signs or short-term flares. Chronic therapy of corticosteroids causes severe side effects like being overweight [67].

**Disease-modifying Antirheumatic Drugs (DMARDs):** DMARDs decrease the succession of RA and stop irreversible erosion of the joints and other soft tissues by intrusive overactivity of the immune system. It is largely successful in the near beginning stages. Adverse effects liver includes marrow and immune suppression.

**Tumour Necrotic Factor Alpha Inhibitors (TNF-Alpha Inhibitors):** TNF-alpha is an inflammation-causing agent. TNF-alpha blockers avoid inflammatory reactions.

Blockers diminish ache, morning rigidity, and inflamed joints [67, 68]. Probable adverse effects comprise elevated threat of infection, blood-related diseases, heart failure, demyelinating disorders.

**Surgery:** Surgery restores injured bones, corrects deformity, and decreases ache.

**Arthroplasty:** It is a complete bone replacement; surgeons take out injured structures and add a metallic or plastic prosthesis [69].

**Tendon Renovate:** If tendons have loosened or ruptured surrounding joints, surgery helps renovate them [70].

**Synovectomy:** This process involves the elimination of the synovial membrane due to inflammation and ache.

**Arthrodesis:** The doctor can combine bones to reduce ache and to steady joints.

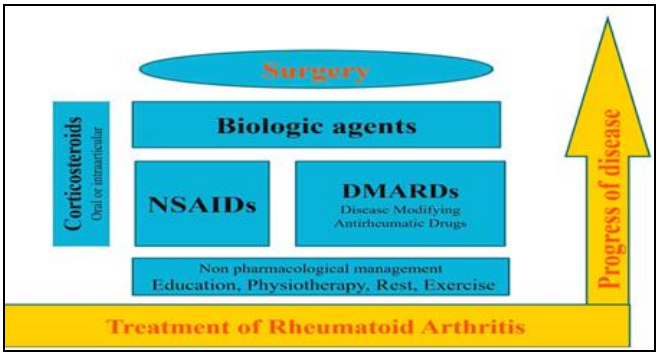


**FIG. 3: TREATMENT OF RHEUMATOID ARTHRITIS**

**Herbal Therapy:** Numerous anti-arthritic agents have been developed and used in RA treatment; still, these agents experience many adverse effects resulting in limited efficacy.

The herbal therapy approach now has a wide variety, usually not seen with artificial agents. Green medicine has been extensively studied as harmonizing and optional agent since the olden days in the alleviation of inflammation and immune system diseases.

The present pharmacotherapeutics administered by conservative formulations give healing profits merely till suboptimal level; therefore take up all the problems in the RA therapy. Green phytoconstituents for RA therapy are given as follows in **Table 1.**

**TABLE 1: HERBAL THERAPY FOR RA 71**

| S. no. | Natural product | Source | Part used | Active principal | MOA and molecular pathways involved | Challenge and adverse effect |
|---|---|---|---|---|---|---|
| 1 | Boswellia Serrate Indian frankincense salai/ salaigu gglu | The resin of Boswellia | Oleo gum resin from the trunk of the tree | Triterpenic acid that is b- Boswellic acid acety b- Boswellic acid 11 keto b-Boswellic acid and acetyl 1-keto-b- b-Boswellic acid | Acts via 5-LOX inhibition | Stomach pain, nausea diarrhoea and allergic rashes reported |
| 2 | Turmeric Curcumin Curcuma L onga | Curcuma Longa Linn | Dried as well as fresh rhizome | Curcumin | It acts by inhibition of COX, 5-LOX and glutathione S-transferase | Higher dose long term administration causes nausea and diarrhea |
| 3 | Gamma limol (GLA) | Rapeseed canola oil soy beans walnuts and flex seed linseed oil | Plant seed oil | O-mega 6 fatty acids | Dietary GLA it converted directly to DGLA increased levels of DGLA promote the synthesis of in- flammattory metabolites *i.e*, series prostaglandins PGEI suppress chronic inflammation | It is safe at the dose 2.8 g/day up to year besides it causes softening of tools belching and intestinal gas to |
| 4 | Ginger Zingiberoffici n ale | Zingiberoffici nails Linn | Rhizomes | It contains high proportions sesquiterpenes, predominantly zingiberene and gingerols | It inhibits PG and LTs biosynthesis via an inhibitory action on PG synthetase and 5-LOX, and addition to this also inhibits pro-inflammatory cytokines such as IL 1 TNF, and IL-8 | It is safe, but some minor side effects such as heartburn diarrhoea, stomach discomfort, and skin irritation may take place |
| 5 | Thunder God vine | Tripteryguim wifordii | Skinned root (extract) | Its major compositions are di-terpenoid triptolide | It interferes with the production of PGs cytotoxic T-cell proliferation and IL-2 too | GIT disturbances such as nausea, abdominal pain, indigestion flatulence, constipation, hair loss male |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | infertility, and significant immune suppression |
| 6 | Celastrol | Tripteryguim wil for dii (lei gong teng thunder of god vine), which belongs to the Celastraceae family | Root and work | A yellow quinoidenor triterpene called Celastrol which is a pentacyclic triterpene | Celastrol has beneficial antiaarthritic effects by suppersion of pro-inflammatory cytokines mediated MMP-9 expression and lipopolysachardies | Diarrhoea headache nausea, and infertility, especially at high dose |
| 7 | Thymoquinone (TQ) | TQ is obtained from the volatile oil of black the black caraway seed *Nigella sativa* Ranuunculaaceae family | Volatile oil of the black seed | TQ is a major bioactive it constituent of the volatile oil og black seed (54%) | It extracts antiarrhritic action against carrageenan induced paw oedema in rats by inhiniting the inflammatory mediators | It is safe and may cause allergic rashes |
| 8 | Sinomenine | It is obtained from the root of Sinomenine Actum | Roots | Sinomenine is alkaoid | Sinomenine may inhibit proliferation of synovial fibroblasts in arthritis | It produces abnormal immunosuppression |
| 9 | Paeoniflorin | It is obtained from the root of a Paeonia | Roots | It is a major constituent of paeonialacflora | It extracts anti-arthritic action by inhibition of IL-6 and COX-2 | Abdiminal upset and skin Rashes |
| 10 | Asiatocide and madecesso side | Two whole plants of cebtellaasiatica | whole pant | It contains large amounts of pentacyclic triterpenoid, including asiatico and madecassoside | It provides production against joint destruction in CIA mice | Skin allergy, burring sensations, headache nausea, extreme drowsiness and contact dermatitis |
| 11 | Epigallocatechin | It is obtained from oldenlandia Diff uss and fruits zizphusjujube | Fruit | Epigallocatechin gallate also know as epigallocatachin 3-gaalate ia an ester of epigallocatachin and gallic acid | It showed effective action against arthritis by TNF, an inhibition | It hampered iron absorption in a dos-dependent |
| 12 | Naringin | It is obtained from grapes and citrus fruits | Grapes and citrusfruit | Naringin is a flavanone-7-O-glycoside | It showed antiiarthritic action by suppression of MMP-9 | Biiter and taste |
| 13 | Hesperidin | It is obtained from the fruit of citrus aurrations | Citrus fruits | Flavanone glycoside | It suppression the T-lymphocyte proliferation and IL-2 production in rats too | Limited bioavailability |
| 14 | Resveratrol | It is obtained from grapes and redn wine | Grapes red wine and berries | Resveratrol polyphenolic compounds | It mediated antiarthritic action by targeting NF-Kb and simultaneously decreases AGEs-stimulated expression and prevent AGEs- mediated destruction of CLA | Poor oral bioavailability |

AA, adjuvant arthritis; AGE, advanced glycation end products; CIA, collagen-induced arthritis; COX, cyclooxygenase; DGLA, dietary gammalinolenic acid; GLA, gammalinolenic acid IL, inter-leukin; MMP-9, metalloprotieinase-9; MOA, mechanism of action, NF-KB, nuclear factor- KB; TNF; tumour necerosis factor-a.

**CONCLUSION:** RA is an assorted disorder, and the response to therapy is unpredictable. DMARDs must be used almost immediately following diagnosis; methotrexate is a top early drug; illness ought to be often monitored; a combination of green medicine with synthetic drugs decreases the progression of the disease.

There is a restoration of attention in indigenous natural agents due to the prevalent faith that plant products are more harmless and reliable than expensive artificial medicines. In outlook, extra synchronized multidimensional research is required to correlate botanical and phytochemical properties to precise pharmacological activity in RA therapy. It is trusted that coming years will observe a drastic swing in how medical studies are conceived in RA.

**ACKNOWLEDGEMENT:** Nil

**CONFLICT OF INTEREST:** Authors declare no conflict of interest.

## REFERENCES:


1. Heidari B: Rheumatoid Arthritis: Early diagnosis and treatment outcomes. Caspian Journal of internal medicine. 2011; 2(1): 161.
2. Bullock J, Rizvi SA, Saleh AM, Ahmed SS, Do DP, Ansari RA and Ahmed J: Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice 2018; 27(6): 501-7.
3. Goode JD: Textbook of Orthopaedic Medicine. Treatment by Manipulation, Massage and Injection. Annals of the Rheumatic Fiseases 1978; 37(1): 105.
4. Ormseth MJ, Yancey PG, Solus JF, Bridges Jr SL, Curtis JR, Linton MF, Fazio S, Davies SS, Roberts LJ, Vickers KC and Kon V: Effect of Drug Therapy on Net Cholesterol Efflux Capacity of High-Density Lipoprotein–Enriched Serum in Rheumatoid Arthritis. Arthritis & Rheumatology 2016; 68(9): 2099-105.
5. Peeters Y: Mind the gap: explanations for the differences in utilities between respondent groups. Department of Medical Decision Making, Faculty of Medicine/Leiden University Medical Center (LUMC), Leiden University; 2011; 11.
6. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Yoshida S and Graham RR: Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 2014; 506(7488): 376-81.
7. Karouzakis E, Neidhart M, Gay RE and Gay S: Molecular and cellular basis of rheumatoid joint destruction. Immunology Letters 2006; 106(1): 8-13.
8. Lee KP, Sudjarwo GW, Kim JS, Dirgantara S, Maeng WJ and Hong H: The anti-inflammatory effect of Indonesian Areca catechu leaf extracts *in-vitro* and *in-vivo.* Nutrition Research and Practice 2014 Jun; 8(3): 267-71.
9. Murugananthan G and Mohan S: Anti-inflammatory and anti-arthritic activities of Delonixelata bark extracts. Int J of Res in Ayur and Pharm 2011; 2(6): 1819-21.
10. Fatima NI and Fatima SJ: Pharmacological screening for anti-arthritic activity of *Moringa oleifera*. Asian J Pharm Clin Res 2016; 9(3): 106-11.
11. Iqbal S and Rattu MA: Review of Rheumatoid Arthritis. US Pharm 2019; 44(1): 8-11.
12. RA SO, Relief S and Work HN: Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints.
13. Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH and Curtis JR: 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis & Rheumatology 2016; 68(1): 1-26.
14. Minichiello E, Semerano L and Boissier MC: Time trends in the incidence, prevalence, and severity of rheumatoid arthritis: a systematic literature review. Joint Bone Spine 2016; 83(6): 625-30.
15. Aletaha D and Smolen JS: Diagnosis and management of rheumatoid arthritis: a review. Jama 2018; 320(13): 1360-72.
16. Aletaha D and Smolen JS: Does Triple Conventional Synthetic Disease-Modifying Antirheumatic Drug Therapy Improve upon Methotrexate as the Initial Treatment of Choice for a Rheumatoid Arthritis Patient. Rheumatic Disease Clinics 2019; 45(3): 315-24.
17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD and Combe B: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism 2010; 62(9): 2569-81.
18. Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, Van Der Heijde D, Dougados M, Van Vollenhoven R, Bijlsma JW, Burmester GR and Scholte-Voshaar M: Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Annals of the rheumatic diseases. 2017; 76(6): 1101-36.
19. Van Ede AE, Laan RF, Rood MJ, Huizinga TW, Van De Laar MA, Denderen CJ, Westgeest TA, Romme TC, De Rooij DJ, Jacobs MJ and De Boo TM: Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: A forty-eight–week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 2001; 44(7): 1515-24.
20. Fala L: Kevzara (Sarilumab), a New IL-6 Receptor Antagonist Approved for Moderately to Severely Active Rheumatoid Arthritis.
21. Fala L: Olumiant (Baricitinib) Once-Daily Oral Drug Approved for the Treatment of Patients with Moderately to Severely Active Rheumatoid Arthritis.
22. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002; 4(3): 265–72.
23. Van der Linden MP, et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum 2010; 62: 3537–46.
24. Moura CS: Early medication use in new-onset rheumatoid arthritis may delay joint replacement: results of a large population-based study. Arthritis Res. Ther 2015; 17: 197.
25. Cho SK: Factors associated with time to diagnosis from symptom onset in patients with early rheumatoid arthritis. Korean J Intern Med 2017; 113.

26. Raza K: Delays in assessment of patients with rheumatoid arthritis: variations across Europe. Ann Rheum Dis 2011; 70: 1822–25.
27. Ometto F: Methods used to assess remission and low disease activity in rheumatoid arthritis. Autoimmun. Rev 2010; 9: 161–64.
28. Grennan DM, Gray J, Loudon J and Fear S: Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 2001; 60: 214–17.
29. Nishimura K: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007; 146: 797–808.
30. Bizzaro N: Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Res Ther 2013; 15: 16.
31. Malmstrom V, Catrina AI and Klareskog L: The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nat Rev Immunol 2017; 17: 60–75.
32. Padyukov L: A genome-wide association study suggests contrasting associations in ACPA-positive versus ACPA-negative rheumatoid arthritis. Ann Rheum Dis 2011; 70: 259–65.
33. Schuerwegh AJ, et al. Evidence for a functional role of IgEanticitrullinated protein antibodies in rheumatoid arthritis. Proc. Natl Acad. Sci. USA. 2010;107:2586–2591.
34. vanDongen H: Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007; 56: 1424–32.
35. Sellam J: B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: a six-month, national, multicenter, open-label study. Arthritis Rheum 2011; 63: 933–38.
36. Seegobin SD: ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. Arthritis Res Ther 2014; 16: 13.
37. Raychaudhuri S: Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet 2012; 44: 291–96.
38. Okada Y: Risk for ACPA-positive rheumatoid arthritis is driven by shared HLA amino acid polymorphisms in Asian and European populations. Hum Mol Genet 2014; 23: 6916–26.
39. Mori M, Yamada R, Kobayashi K, Kawaida R and Yamamoto K: Ethnic differences in allele frequency of autoimmune-disease-associated SNPs. J Hum Genet 2005; 50: 264–66.
40. Nabi G: Meta-analysis reveals PTPN22 1858C/T polymorphism confers susceptibility to rheumatoid arthritis in Caucasian but not in Asian population. Autoimmunity 2016; 49: 197–10.
41. Goh LL: NLRP1, PTPN22 and PADI4 gene polymorphisms and rheumatoid arthritis in ACPA-positive Singaporean Chinese. Rheumatol Int 2017; 37: 1295–02.
42. McCarthy C: Brief report: genetic variation of the alpha1 -antitrypsin gene is associated with increased autoantibody production in rheumatoid arthritis. Arthritis Rheumatol 2017; 69: 1576–79.
43. Castaneda-Delgado JE: Type I interferon gene response is increased in early and established rheumatoid arthritis and correlates with autoantibody production. Front Immunol 2017; 8: 285.
44. Ding B: Different patterns of associations with anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis in the extended major histocompatibility complex region. Arthritis Rheum 2009; 60: 30–38.
45. Schiff MH: Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients: patient-reported outcomes from multiple controlled and open-label extension studies. Drugs Aging 2006; 23: 167–78.
46. Frisell T: Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. Arthritis Rheum 2013; 65: 2773–82.
47. Kuo CF: Familial aggregation of rheumatoid arthritis and co-aggregation of autoimmune diseases in affected families: a nationwide population-based study. Rheumatology 2017; 56: 928–33.
48. Svendsen AJ: On the origin of rheumatoid arthritis: the impact of environment and genes--a population based twin study. PLoS ONE 2013; 8:57304.
49. Hensvold AH: Environmental and genetic factors in the development of anticitrullinated protein antibodies (ACPAs) and ACPA-positive rheumatoid arthritis: an epidemiological investigation in twins. Ann Rheum Dis 2015; 74: 375–80.
50. Van der Woude D: Gene-environment interaction influences the reactivity of autoantibodies to citrullinated antigens in rheumatoid arthritis. Nat Genet 2010; 42: 814–16.
51. Stolt P: Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann Rheum Dis 2010; 69: 1072–76.
52. Mohamed BM: Citrullination of proteins: a common post-translational modification pathway induced by different nanoparticles *in-vitro* and *in-vivo*. Nanomedicine. 2012; 7: 1181–95.
53. Too CL: Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case-control study. Ann Rheum Dis 2016; 75: 997–1002.
54. Watkin LB: COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nat Genet 2015; 47: 654–60.
55. Klareskog L: A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006; 54: 38–46.
56. Meng W: DNA methylation mediates genotype and smoking interaction in the development of anti-citrullinated peptide antibody-positive rheumatoid arthritis. Arthritis Res Ther 2017; 19: 71.
57. Konig MF: Aggregatibacteractinomycetemcomitans-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Sci Transl Med 2016; 8: 369 ra176.
58. Wegner N: Peptidylarginine deiminase from Porphyromonasgingivaliscitrullinates human fibrinogen and alpha-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum 2010; 62: 2662–72.
59. Khandpur R: NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. Sci Transl Med 2013; 5: 178-40.
60. Alspaugh MA, Henle G, Lennette ET and Henle W: Elevated levels of antibodies to Epstein-Barr virus

antigens in sera and synovial fluids of patients with rheumatoid arthritis. J Clin Invest 1981; 67: 1134–40.
61. Wu X: Molecular insight into gut microbiota and rheumatoid arthritis. Int J Mol Sci 2016; 17: 431.
62. Chen J: An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. Geno Med 2016; 8: 43.
63. Gan RW: The association between omega-3 fatty acid biomarkers and inflammatory arthritis in an anti-citrullinated protein antibody positive population. Rheumatology 2017; 56: 2229–36.
64. Hu Y: Long-term dietary quality and risk of developing rheumatoid arthritis in women. Ann Rheum Dis 2017; 76: 1357–64.
65. Orellana C: Oral contraceptives, breastfeeding and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis 2017; 76: 1845–52.
66. Alpizar-Rodriguez D: Female hormonal factors and the development of anti-citrullinated protein antibodies in women at risk of rheumatoid arthritis. Rheumatology 2017; 56: 1579–85.
67. Van der Woude D: Epitope spreading of the anti-citrullinated protein antibody response occurs before disease onset and is associated with the disease course of early arthritis. Ann Rheum Dis 2010; 69: 1554–61.
68. Krishnamurthy A: Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss. Ann Rheum Dis 2016; 75: 721–29.
69. Wigerblad G: Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism. Ann Rheum Dis 2016; 75: 730–38.
70. Pianta A: Two rheumatoid arthritis-specific autoantigens correlate microbial immunity with autoimmune responses in joints. J Clin Invest 2017; 127: 2946–56.
71. McInnes IB and Schett G: The pathogenesis of rheumatoid arthritis. N Engl J Med 2011; 365: 2205–19.
72. Rahman M, Beg S, Verma A, Al Abbasi FA, Anwar F, Saini S, Akhter S and Kumar V: Phytoconstituents as pharmacotherapeutics in rheumatoid arthritis: challenges and scope of nano/submicromedicine in its effective delivery. Journal of Pharmacy and Pharm 2017; 69(1): 1-4.

**How to cite this article:**
Banu S and Varghese L: A review on herbal drugs with potential anti-arthritic activity. Int J Pharm Sci & Res 2021; 13(4): 1479-87. doi: 10.13040/IJPSR.0975-8232.13(4).1479-87.