Bangladesh Pharmaceutical Journal ***25****(2): 125-136, 2022 (July)*

Important Medicinal Plants Recommended in Management of Rheumatoid Arthritis

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(Manuscript received: March 18, 2022; Accepted: May 19, 2022; Published (web): July 30, 2022)

Abstract

Rheumatoid arthritis (RA) is one of the most commonly occurring autoimmune disorders in both men and women. Management of RA is posing challenge to the modern medicine practice. Non-management of RA is associated with both articular and extrarticular complications. Currently, immuno-modulators and immune-suppressants are the mainstay of therapy. However their use is limited due to severe consequences. Present systematic review is carried out to identify potential herbs and herbal preparations claimed to have anti-arthritis properties. Findings of our study shows that leaves, barks and root parts of the plants are the most commonly associated to have anti-rheumatism effect. Most of the plants studies belongs to lamiaceae, leguminosae, malastomataceae, cobretaceae and apocynaceae families. These plant preparations commonly producing their effect through inhibition of IL-1, IL-6, IL-1ß, cytokines and cyclooxygenase. The effect is also mediated through TNF-α, ROS, NF-KB, prostaglandin and leukotriene. Based on these results we recommend that there are some promising number of plants and plant preparations which may be explored further to find out a novel and effective therapy for RA having unique mechanism of action. These may be used as adjunct therapies or nutritional supplements in the treatment of arthritis.

Key words: Rheumatoid arthritis, arthritis, herbal therapy, management, plant preparation, medicinal plants.

Introduction

The word arthritis is derived from the Greek words ‘‘artho’’ meaning joint and ‘‘itis,’ meaning inflammation, respectively (Daily *et. al*. 2016)**.** Rheumatoid arthritis (RA) is one of the most common autoimmune inflammatory disease, characterized by synovitis, systemic inflammation and generation of autoantibodies (Lee *et.al.* 2018, Zhou *et.al.* 2018). RA mainly affects the diarthrodial joint, which leads to impaired joint function, severe pain and reduced life expectancy (Aloke *et.al.* 2019, Chang *et.al.* 2010). Recent epidemiological study shows that about all over the world rheumatoid arthritis affected 1% of people. Moreover, RA affects women more widely than men (Dudics *et.al.* 2018).

RA leads to different symptoms like exterior changes involving joint malformation, swelling, and joint dysfunction, while interior pathological changes mainly involve synovial hyperplasia and cartilage destruction. All of these changes are convoyed by systemic inflammatory responses involving many cytokines, such as tissue necrosis factor – alpha (TNF-α) and interleukin-6 (IL-6) (Zhu *et.al* 2018). A major contributor in the pathogenesis of RA is pro-inflammatory cytokines such as interferon gamma (IFN-γ), interleukin (IL)-1β, IL-18, IL-6, IL-22, GM-CSF and TNF which are found to be raised during the development of arthritis. These pro-inflammatory cytokines activate cells in their local environments and continue the production of cytokines, this in turn

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DOI: https://doi.org/10.3329/bpj.v25i2.60964

creates a positive feedback for synoviocyte to perpetuate synovial inflammation that ultimately leading in the destruction of joints and functional impairments (Pablo-Pérez *et. al.* 2018, Liu *et. al.* 2016).

Pathogenesis of RA: The pathogenesis of RA clearly reveals that it is an autoimmune disease which involves the active role of IL-17, 18 and RANKL. The release of these chronic inflammatory mediators cause destruction of synovial membrane, cartilage, collagen and other surrounding tissues. This will lead to formation of pannus and fibrosis affecting mobility of joint called ankylosis. The ankylosis leads to thickening of synovial membrane and erosion of cartilage. This affects the space present between the joints. The whole joint get swollen and cause pain while movement (Kaur *et.al.* 2012).

Current therapy: Early diagnosis of RA is the important key for the desirable outcomes (reduced joint destruction, less radiologic progression and no functional disability) as well as cost effective. Early diagnosis heavily relies on the clinical information that gathered from the patient's history and physical examination supported by blood tests, and imaging analysis (Guo *et.al.*2018)**.** Paracetamol**,** ibuprofen, diclofenac and other NSAIDs, steroids and disease modifying anti-rheumatoid drugs, biologicals such as TNF-α and IL antagonists and JANUS kinase inhibitors (JKIs) are the main drugs used for RA management in the clinic to relieve pain and lessen immunological reaction mediated inflammation and joint damage (Ruckmani *et.al.* 2018). According to study, about 30–50% of patients do not effectively respond to these drugs due to various adverse effects, including hepatotoxicity and myocardial infraction. Approximately 20% of patients taking long-term NSAIDs have gastrointestinal (GI) toxicity with upper GI adverse effects such as perforation, ulceration and bleeding (Zhuang *et al.* 2017, Vetal *et. al.* 2013). So, there is still a need to seek for safer drugs with lower side effects that can be used for long-term administration in the management of rheumatoid arthritis (Rathi *et.al.* 2013, Chinnasamy *et.al.* 2019).

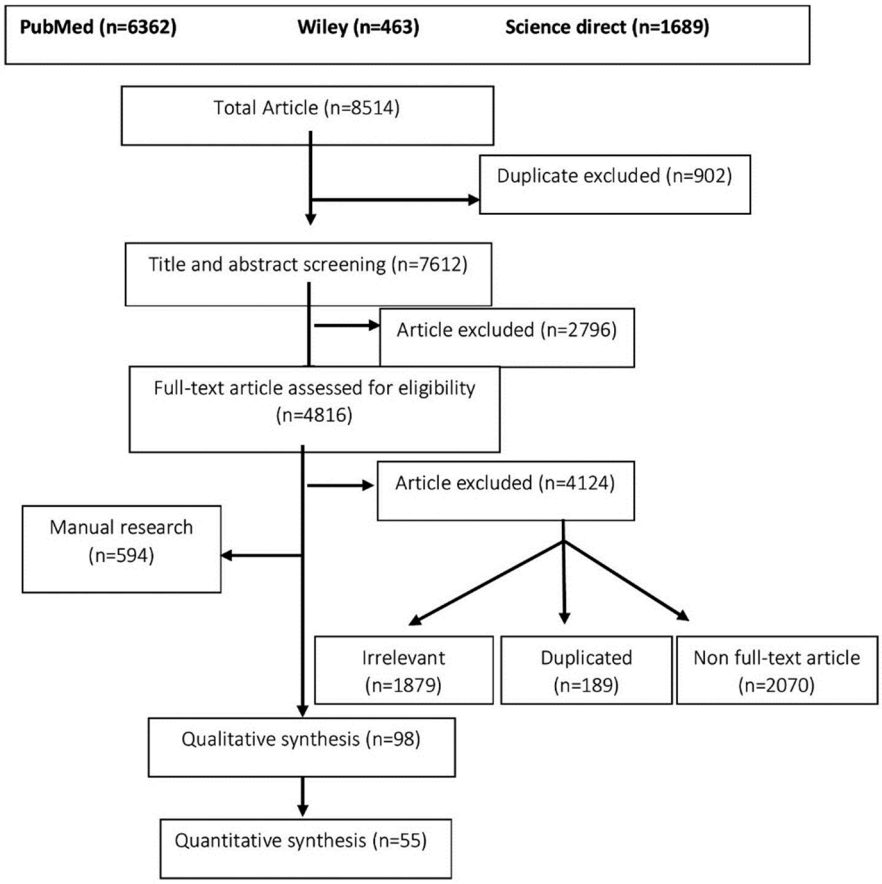
Importance of herbal therapy: Undesirable side effects often force the patients to look for complementary and alternative medicine (CAM). Higher plants in Himalayan region is the treasure house of natural wealth for medicinal and aromatic plants. Numerous wild and cultivated plants are used by the Indian traditional healers because of their convenience, adequacy, affordability and high-safety profile for the past many centuries to treat various ailments such as asthma, diabetes, snake bite, diarrhoea, indigestion, fever, jaundice, etc. (Al-Nahain *et al.* 2014, Erhirhie *et.al.* 2019). According to W.H.O, about 80% of the world population have faith on natural drugs (Narendhirakannan *et al.* 2007). NCCAM (National Centre for Complementary and Alternative Medicine) suggests that "Complementary and alternative medicine (CAM) is a group under which different medical and health care systems, practices, and products and are not part of conventional medicine at present". Arthritis is one of the leading diseases for which CAM is a best option. However, more than 70% of patients using CAM modalities never mention these products to their physicians (Efthimiou 2010).

Methodology

Publication regarding rheumatoid arthritis and effective plants were extracted form databases such as Science Direct, Wiley and PubMed. Keywords used in this study included "use of herbal drug in the management of rheumatoid arthritis", "use of herbal drug in the management of rheumatoid arthritis by a cell culture method", "use of natural immunomodulators in the management of rheumatoid arthritis". Out of the 8514 collected articles (published till 26 June 2020), 8425 were excluded due to duplication, non-relevance, other than English language or lack of access to the original article.

Inclusion and exclusion criteria: The search was restricted to English language articles only. All studies found during the search were independently evaluated for competence and inclusion by two different authors. After compliance with inclusion criteria and experimental research that evaluate the

effects of medicinal herbs or plant components in rheumatic animals or patients were included in the current research. Irrelevant studies or original article that evaluated mixed plant extracts, algae, or mushroom extracts were also excluded.



Results

Plant name	Active part and preparation	*In vitro* and *in vivo* method	Mechanism of action
Orthosiphon stamineus (Tabana *et al.* 2016) Lamiaceae	Leaves maceration	Cell proliferation, cell viability and cytokine analysis. Acute, sub-chronic and chronic in vivo models. FCA-induced arthritis in rats and fluorescence molecular tomography.	Significant reduction of TNF-α, IL-1.
Trichilia monadelpha (Ben *et al.* 2017) Meliaceae	Stem bark soxhlet extraction	CFA-induced arthritis.	Reducing bone tissue damage and resorption.
Ipomoea batatas L. (Majid *et al.* 2018) Convolvulaceae	Tubers and roots maceration	CFA Carrageenan croton oil-induced ear edema constraint.	Inhibition of free radicals in vitro and inhibition of TNF-α and IL-1β, IL-2, IL-6 and NO mainly contributes in the inflammation during the early and the late phase of edema.

Aristolochia Bracteata (Chitme 2009) Aristolochiaceae	Whole plant soxhlet extraction	Freund's complete adjuvant, xylene-induced ear edema in mice.	Inhibiting cytokines and leukotriene infiltration.Inhibitory effect on phospholipase A2 and prostaglandin.
Platycodon grandiflorum (Kwon *et al.* 2014) Campanulaceae	Root extraction	Collagen induced arthritis and splenocyte.	Inhibit cytokines, TNF-α and IL-6.
Eysenhardtia polystachya (Pablo-Pérez *et al.* 2018) Fabaceae	Bark maceration	CFA	Decreased the serum levels of pro-inflammatory cytokines IL-6, TNF-α, and GM-CSF.
Myricaria bracteata (Zhuang *et al.* 2017) Tamaricaceae	-	CIA mice. AIA rats and murine macrophage isolation and culture.	Blocking the expression of TNF-alpha and IL-1b in the serum. Blocking the expression of IL-6 and IL-1b. Inhibitory effect on MAPK and NF-kb pathway
		Lipopolysaccharide-induced, NO and pro-inflammatory mediators production, and iNOS expression.	Inhibit TNF-a, and IL-6 secretion. Inhibitory effect on MAPK and NF-kb pathway.
Plectranthus amboinicus (Chang *et al.* 2010) Lamiaceae	Whole plants extraction	Collagen-induced arthritic rat.	Inhibit TNF-a, IL-6 and IL-1b.
Garcinia indica (Warriar *et al.* 2018) Clusiaceae	Fruits soxhlet extraction	CFA, stair climbing test.	Inhibit NF-κb in the articular chondrocytes and thus suppressing the inflammatory cascade, reduce the paw swelling, arthritis index and hyperaglesic response.
Oldenlandia diffusa (Zhu *et al.* 2018) Rubiaceae	Powder/ herbs decoction	CFA and incomplete Freund's adjuvant.	Decrease the expression of TNF-$\alpha$and IL-6 by moderately inhibitory effect on the activation of NF-κB.
Periploca forresti (Liu *et al.* 2016) Apocynaceae	Roots maceration	CFA-induced arthritis.	Suppressing STAT3 signaling and reducing the levels of RA factors IL-6, Th2 cytokines (TGF-β1 and IL-13), Th1 (IFN-γ and IL-33), and Th17 (IL-22) and inhibits the expression of GATA3, T-bet, and C-Jun.
Panax ginseng (*Zhang et al.* 2017) Araliaceae	Root	CFA-induced arthritis.	Inhibited TNF-α and IL-6 concentration via up-regulation of PPAR-γ expression and subsequent inhibition of NF-κb signal pathway.
Plumeria alba (Choudhary *et al.* 2014) Apocynaceae	Leaves soxhlet extraction	Formaldehyde-induced arthritis, CFA-induced arthritis.	Inhibited TNF-α, IL-1β, and PDGF.
Copaifera salikounda (Chinyere *et al.* 2019) Leguminosae	Seed pods maceration	CFA induced arthritis.	Attenuated inflammatory mediators (TNF□α and IL□1β, IL□6, IL□15, IL□18, and leukotriene B4), haematological (leucocytes), and oxidative stress (ROS) parameters.
Cinnamomum zeylanicum (Rathi *et al.*		Carrageenan-induced rat paw edema, Cotton pellet-induced	Suppress PGE2, COXs and TNF-α and IL-1.

2013) Lauraceae	Bark	granuloma, AIA. Concanavalin (cona)-stimulated lymphocytes.	Inhibit cytokines (IL-2, IL-4, and IFN γ).
Eucommia ulmoides (Wang *et al.* 2018) Eucommiaceae	NA	Collagen-II induced arthritis.	Improving RANKL/OPG ratio and decreasing NF-κB pathway.
Acanthopanax senticosus Harms (Takahashi *et al.* 2014) Eleutherococcus	Shrub extraction	Collagen-induced arthritis.	Reduction of ROS, inhibition of cytokine production is required to prevent arthritis.
Premna serratifolia (Rajendran 2010) Lamiaceae	Fresh wood soxhlet extraction	Freud's adjuvant induced arthritis.	Reducing WBC count due to the release of IL-IB.
Berberis orthobotrys (Alamgeer *et al.* 2017) Berberidaceae	Roots cold maceration	BSA turpentine oil induced joint edema, formaldehyde induced arthritis, CFA induced arthritis. HRBC membrane stabilization.	Impediment of pro-inflammatory mediators. Inhibit the production of inflammatory mediators i.e., IFN α, PDGF and cytokines (IL-1, IL 6 and TNF-α). Interfering action on the release of neutrophils lysosomal content.
Melastoma malabathricum Linn (Kumar *et al.* 2016) Melastomataceae	Leaves soxhlet extraction	CFA-induced arthritis, molecular docking studies.	Decreased the serum levels of IL-1β, TNF-α and IL-6.
Cleome gynandra L. (Narendhirakannan *et al.* 2007) Cleomaceae	Leaves soxhlet extraction	Adjuvant-induced arthritis.	Retard complications and spread of the inflammatory process by reducing the destruction of TNF-α.
Smilax glabra Roxb. (Dong *et al.* 2017) Smilacaceae	Rhizome soxhlet extraction	CFA	Decreased serum levels of cytokines TNF-α, IL-1β, and IL-6. Inhibiting the tlrs-mediated NF- κB signalling.
Moringa oleifera (Mahdi *et al.* 2018) Moringaceae	Leaves extraction	Complete Freund's adjuvant (CFA)-induced arthritis.	Inhibition of NO; decrease in serum level of IL-1, IL-6, TNF-a; inhibition of COX2 path-way by inhibition of PGE2 production.
Trachyspermum ammi (Qamar *et al.* 2020) Umbelliferae	Seed maceration	Collagen type-II arthritic model, complete Freund's adjuvant.	Reduced the inflammation and oxidative stress.
Pistia stratiotes (Koffuor 2012) Araceae	Leaf soxhlet extraction	Adjuvant-induced arthritis.	Suppressed joint inflammation.
Achyranthes aspera (Chinnasamy *et al.* 2019) Amaranthaceae	Leaves maceration	Formaldehyde induced arthritis.	Suppression of inflammatory mediator. Block the COX2 pathway.

Terminalia tomentosa (Jitta *et al.* 2019) Combretaceae	Bark maceration, soxhlet extraction	Carrageenan induced inflammatory model and Freund's adjuvant-induced arthritis model.	Attenuating the effects of serotonin and histamine release during acute inflammation. Immunosuppressive effects.
Tamarindus indica (Sundaram *et al.* 2015) Fabaceae	Seed extraction	Adjuvant-induced arthritis.	Inhibiting MMPs hyaluronidases, exoglycosidases cathepsins, IL-1β, TNF-α, IL-6, IL-23, COX-2 AND TRAP.
Dryopteris filix-Mas (Erhirhie *et al.* 2019) Dryopteridaceae	Leaves maceration	Egg-albumin-induce paw edema, formaldehyde-induced arthritis, xylene-induced topical edema.	Inhibit inflammatory mediators such as histamine, serotonin, prostaglandin and bradykinin.
Avicennia marina (Gandomani 2014) Verbenaceae	Leaves maceration	Complete Freund's adjuvant-induced arthritis	Reduced the level of IL-1β, IL-6, and TNF-α.
Polygonum orientale (Gou *et al.* 2017) Polygonaceae	Stems and leaves decoction	Xylene induced ear edema, Carrageenan induced paw edema, FCA - induced arthritis, formaldehyde induced arthritis.	Inhibit pro-inflammatory mediators, prostaglandins, leukotriene, bradykinin, TNF-α and IL-1, IL-6, and PGE2 and bone erosion.
Terminalia chebula (Seo *et al.* 2012) Combretaceae	Dried ripe fruits extraction	Complete Freund's adjuvant, enzyme-linked immunosorbent assay, acetic acid-induced.	Levels of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β were reduced significantly and the production of IL-17 was also inhibited.
Bidens bipinnata L. (Shen *et al.* 2015) Asteraceae	Dried aerial parts digestion extraction	Adjuvant-induced arthritis.	Inhibit the elevation of expression of TNF-α, IL-1β and IL-6.
Dissotis thollonii Cogn. (Djuichou *et al.* 2019) Malastomataceae	Fresh leaves maceration	Anti-inflammatory assays, inhibition of protein denaturation, assay of cyclooxygenase and 5-lipoxygenase inhibition.	Inhibition of protein denaturation, 5-LOX, of COX and ROS.
		CFA monoarthritis induced by Zymosan polyarthritis induced by CFA.	Inhibition of TNF alpha.
Saraca asoca (Gupta *et al.* 2014) Detarioideae	Seeds soxhlet extraction	Freund's adjuvant (CFA) arthritis.	Decreasing the level of cytokine and IL, COX 1 and 2.
Jatropha isabellei (Fröohlich *et al.* 2017) Euphorbiaceae	Underground parts maceration	Carrageenan-induced arthritis, chromatographic analyses.	Inhibit lymphocyte proliferation, PKC pathways.
Plumbago zeylanica Linn (Hegde *et al.* 2014) Plumbaginaceae	Root paste	CFA Carrageenan	Mechanism of action is not elucidated.
Holopteleain tegrifolia Roxb (Hegde *et al.* 2014) Ulmaceae	Bark paste		
Cleistopholis patens	Stem bark maceration	CFA-induced	Mechanism of action is not elucidate.

(Aloke *et al.* 2019 Annonaceae		rheumatoid arthritis. Inflammatory parameters • CRP • RF	
Lemon (Tag *et al.* 2014) Rutaceae	Fruit peel infusion	CFA	Reduction in ESR, CRP and cytokines' levels.
Capsicum annuu (Tag *et al.* 2014) Solanaceae	Fruit and leaves	CFA	Reduction in ESR, CRP and cytokines' levels.
Piptadeniastrum africanum (Mbiantcha *et al.* 2017) Leguminosae	Fresh stem bark decoction	CFA-induced arthritis. Isolation of human PMNCs, peritoneal macrophages isolation, Chemiluminescence assay, cytokine assay T-Cell proliferation assay, MTT cytotoxicity assay.	Inhibited considerably the release of TNF-α and IL-1β.
Zingiber officinale (Fouda 2009) Zingiberaceae	Rhizomes maceration	Collagen induced arthritis.	Reduction of IL-1, IL-2, IL-6, or TNF-alpha levels.

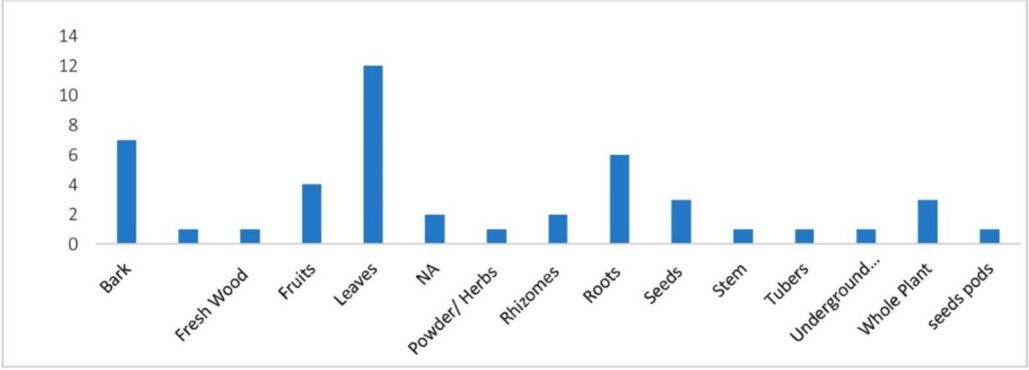


Figure 1. Part of plants used in rheumatoid arthritis.

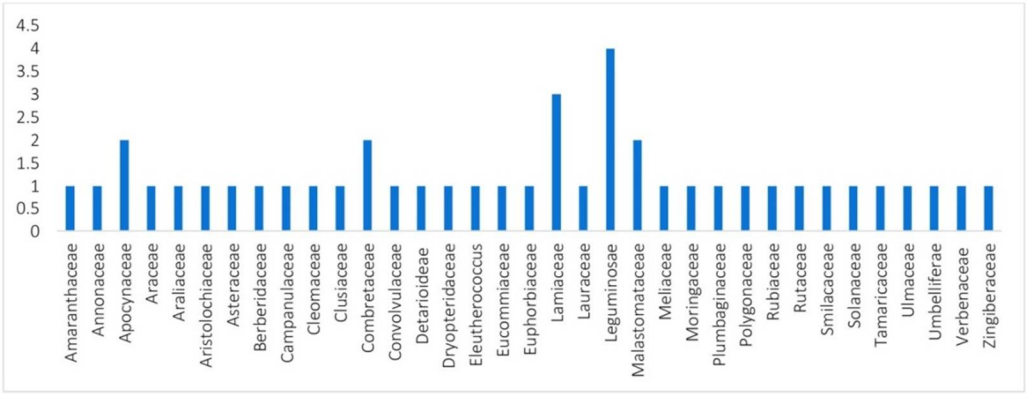


Figure 2. Most explored plant families.

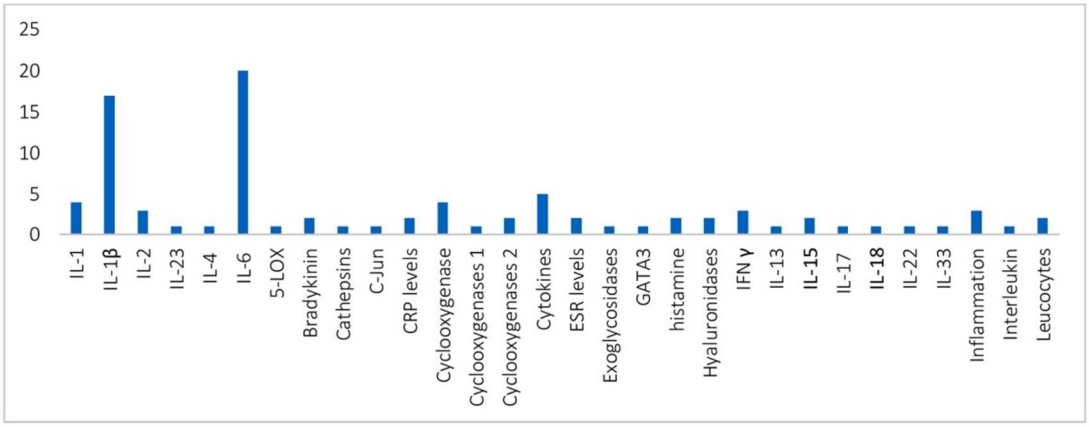


Figure 3(a). Mechanism of action of plants by blocking the mediators.

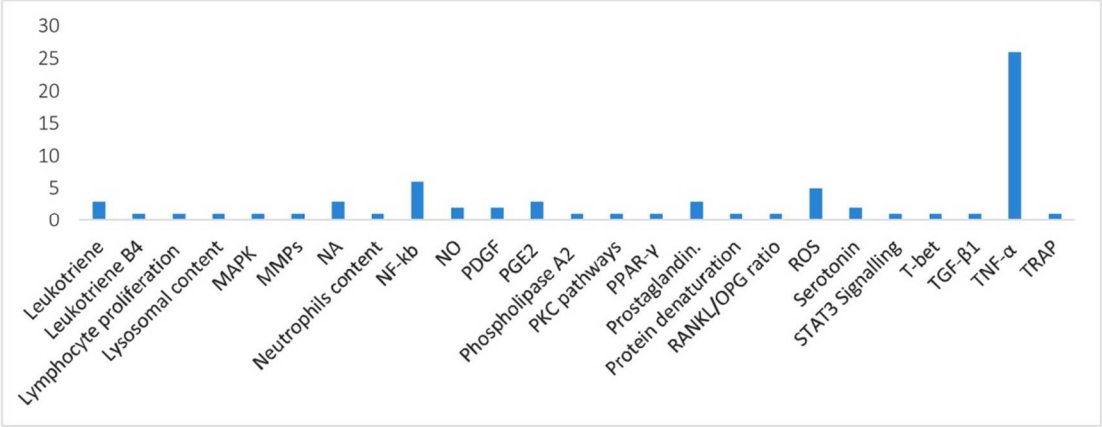


Figure 3(b). Mechanism of action of plants by blocking the mediators.

Conclusion

India have rich floral diversity, with approximately more than 17,000 angiosperm species, 64 gymnosperms, 1,200 pteridophytes, 2,850 bryophytes, and 2,021 lichens. From this only 7,500 species have been reported to have medicinal uses *(*Tabana *et al.* 2016**).** Ayurveda is an ancient and popularly practiced medicinal system in India ((Ben *et al.* 2017**).** The Ayurvedic system of medicine practice in India are vastly dependent on use of medicinal plants in an effective management of various types of arthritis (Kumar *et. al.* 2008). According to study, the data showed that maximum of the world's population use botanic drugs to combat health problems maintenance of life. Flavonoids and hydroxylated phenols has been shown to have response in infection. Flavones and flavanones, have bitter taste and act as natural anti-feedant. Alkaloids are the commonly found plant metabolites. An alkaloid derivative, nicotine has shown an insecticidal activities. Quinine is another alkaloid isolated from the bark of the *Cinchona* tree, was the first active anti-malarial drug (Savant *et al.* 2014). Various primary and secondary metabolites of natural resources are found to have anti-inflammatory properties. Phytochemicals can moderate the expression of pro-inflammatory signals that evidently have potential against arthritis. Research suggests that polyphenols is also used in the treatment of arthritis (Arya *et al.* 2011). Natural anti-arthritic agents act by conquering the various inflammatory mediators like TNFα, IL-1β, COX, LOX, NF-κB, adhesion molecules and metalloproteinases (Bhupinder *et al.* 2017).

We conclude from this study that leaves, barks and root parts of the plants are most commonly associated to have anti-rheumatism properties. Most of the plants studied belong to lamiaceae, leguminosae, malastomataceae, cobretaceae and apocynaceae families. These plant preparations commonly producing their effect through inhibition of cytokines, cyclooxygenase, IL-1, IL-6, and IL-1ß. Their mechanism also involves moderation of TNF-α, ROS, NF-KB, p rostaglandin and leukotriene. Based on these results we recommend that these are some promising number of plants and plant preparations which may be explored further to find out a novel and effective therapy for RA which can be used alone or can be used as adjunct therapy along with current therapies.

Conflict of interest

The author declares no conflict of interest.

Abbreviations

IL: Intraleukin; **TNF-α:** Tumour Necrotic Factor; **ROS:** Reactive Oxygen Species; **COX:** Cyclooxygenase; **LOX:** Lipoxygenase; **NF-κB:** Nuclear factor-κB; **MTT:** 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium; **ESR:** Erythrocyte Sedimentation Rate; **CRP:** C-Reactive Protein; **CFA:** Complete Freund's Adjuvant; **RF:** Rheumatoid Factor; **PKC:** Protein Kinase C; **FCA:** Freund's Complete Adjuvant; **MMPs:** Metalloproteinase; **TRAP:** Tartrate Resistant Acid Phosphatase; **PGE:** Prostaglandins; **Tlrs:** Toll-Like Receptors; **IFN α:** Interferon-α; **PDGF:** Platelet-Derived Growth Factor C; **HRBC:** Human Red Blood Cell; **BSA:** Bovine Serum Albumin; **RANKL/OPG:** Receptor Activator of Nuclear Factor-kb Ligand/ Osteoprotegerin; **AIA:** Adjuvant-induced Arthritis; **PPAR-γ:** Peroxisome Proliferator-Activated Receptors Agonists; **TGF-β1:** Transforming Growth Factor- β1; **Th:** T-Helper cells; **MAPK:** Mitogen-Activated Protein Kinase; **CIA:** Collagen-Induced Arthritis; **GM-CSF:** Granulocyte-Macrophages Colony-Stimulating Factor; **NO:** Nitric Oxide.

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