A review on the efficacy of phytomedicines for Rheumatoid arthritis.

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease marked by inflamed joints causing articular tissue damage and joint dysfunction by triggering the production of auto antibodies. In response to the self epitopes, activation of defense cells, macrophages, occurrence of acute and chronic inflammation of the synovium become major mediators in the progression of RA thereby holds an important prospect for its treatment. As a consequence of the emerging side effects of the popular synthetic drugs like Non-steroidal anti-inflammatory drugs (NSAIDs) and Disease modifying anti rheumatic drugs (DMARDs) available for RA therapy, alternative interventions like herbal therapy or phytomedicines come into play with limited side effects and equivalent effectiveness. Therefore, the discoveries of potential anti-rheumatoid herbal drugs are under great consideration. These herbal interventions are being able to inhibit inflammation, would exhibit substantial benefits including accessibility, less or no toxicity and affordability. The current review retrieved the toxic and chronic side effects of the drugs currently administered for RA therapy along with the need for herbal therapy as an effective alternative approach. Anti inflammatory, anti oxidant and other medicinal properties of some of the easily available herbal plants possessing active phytoconstituents are also been elaborated with scientific evidences collected from various literatures proceeding towards a new pavement for natural drug therapy for RA.

Key words: Rheumatoid arthritis, inflammation, risks, herbal therapy, medicinal plants.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease that is delineated by the inflammation of joints in mostly elderly people. RA is associated with production of auto-antibodies such as "rheumatoid factor" (RF) and anti-citrullinated protein antibodies (ACPA) which causes cartilage and bone damage as well as disability by affecting the synovial joints (Smolen and Steiner, 2003). Other modulator of the immune system including various signaling pathways, cytokines and chemokines plays an essential role in the progression of the disease. Multi-joint symmetry, invasive arthritis and involvement of extra-articular organ are some of the common manifestations of RA. In addition to this, patients also experience drowsiness, fever, depression, pleuritis subcutaneous nodules, peripheral neuropathy and other physical disturbances (Smolen and Steiner, 2003; Firestein and McInnes, 2017). Complications associated with RA include pain, swelling, stiffness and loss of function of joints. Due to the dysregulated immune system resulting in inflammation, the disease is not confined to joints only but is affecting multiple organs like lungs, heart, eyes, kidney and even skin (Abhishek et al., 2017). The contributory factors responsible for the progression of this disease are mainly genetic, epigenetic and environmental. Prevalence of RA is more frequent in women population than in men, occurring between the ages of 35-50 years as reported in 80% of the total cases (Fishman and Bar-Yehuda, 2010). According to the World Health Organization (WHO), the prevalence of
disease varies between 0.3% to 1% in developed countries. For curing this chronic illness, several synthetic drugs including DMARDs are currently been used. These conventional drugs are effectual but usually associated with critical and life threatening adverse effects which diverted the focus towards utilizing phytomedicines as a potential herbal product with minimal side effects.

Plants are the prime sources of medicines since a long time and most of the prescribed medicines have at least one plant derived ingredient in it. In this modern world this utilization of plant extracts and their useful phytochemical compounds gave rise to a new trend of medication known as phytomedicine. This practice of using herbal remedies was known to emerge initially from China followed back then by Indian, Egyptian, Greek, Roman and Syrian. The world is now progressing towards the implementation of herbal medicine or phytomedicines to combat various diseases by repairing and reinforcing the bodily systems specifically the immune system without toxic side effects (Pandey et al., 2011). Recently phytomedicines emerge to be a promising alternative for treating various diseases including RA and their efficacy is relatively comparable with that of commonly used popular drugs. In several in vivo and in vitro experiments, the phytomedicines proved to be effective in RA conditions but their mechanism of action is quite elusive. Moreover there is a scarcity of their potency in clinical studies which needs to be elucidated further. Since a long time traditional herbal medicine are being utilized in several diseases but a clear idea of their mechanistic role need to be explored. Phytomedicines with their various medicinal properties including anti-inflammatory, anti-oxidative, anti-proliferative, immunosuppressive proved to be effective in attenuating RA progression in various experiments. These medicinal plants contain different phyto compounds which targets different signaling pathways reducing the severity of this disease. This review will discuss some selected potential herbal plant species which are considered as potent phytomedicine in suppressing RA pathogenesis.

CURRENT TREATMENT FOR RA AND ITS LIMITATIONS

The treatment for RA involves medication in coalition with proper rest, exercise, adequate knowledge and in severe cases surgery. Currently available treatment includes mainly NSAID's, DMARD's and Anti-TNF (Tumor necrosis factor) biologics (which are a class of DMARDs). NSAIDs and corticosteroids are the first line treatment drugs; they reduce pain and inflammation. NSAIDs include acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin) and etodolac (Lodine) (Bullock et al., 2019). The newer NSAID, celecoxib (Celebrex) is a selective cyclooxygenase-2 (Cox-2) inhibitor that poses lower risk of GI (Gastrointestinal) side effects (Ong et al., 2007). Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. DMARDs are considered as the second line treatment drug. The mainstay of DMARD therapy is methotrexate, which is administered weekly, either orally or subcutaneously. Hydroxychloroquine (Plaquenil), Sulfasalazine (Azulidine), Gold salts, such as aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine) and D-penicillamine (Depen and Cuprimine) are few other DMARDs that are used in RA therapy (Bullock et al., 2019). Biologics, also known as biological DMARDs, acts rapidly and are very effective in retarding the progression of the joint damage caused by RA. They are considered to be a more “direct, defined and targeted” method of treatment (Shiel, 2017). Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab pegol (Cimzia) are all TNF inhibitors that prevent the recruitment of the cells that cause inflammation, bringing rapid symptom relief (Roux et al., 2006). They are recommended if other second-line medications are not effective. Unfortunately, these medications tend to be very expensive and their role in treating patients at various stages of RA and with various mechanisms of action is a matter of continuous investigation.

Despite the advancement in the techniques, the treatment of these drugs are slow progressing and exhibit limited efficiency and have adverse effects (some drugs along with their associated complications are listed in Table 1). RA itself confers an elevated risk of infection, and DMARD and biologic therapies suppress the immune system through various targets, also increasing this risk (Mushtaq et al., 2010) making the body susceptible to various infections. Bacterial infections particularly pneumonia and soft-tissue infections are increased with the use of methotrexate and this are increased 2-4-fold with the addition of an anti-TNF medication (Emery et al., 2008). Similar infectious risks have been found with other biologic DMARDs as well (Emery et al., 2008; Genovese et al., 2008). A significant risk of reactivation of tuberculosis has also been noted with anti-TNF medication. An increased risk of viral infections with traditional or biologic DMARDs, including varicella-zoster virus, Epstein-Barr virus and cytomegalovirus has been documented (Kim, 2010). Hepatitis B and C reactivation have also occurred with biologic DMARDs, so screening prior to treatment and vaccination when possible is recommended (Roux et al., 2006; Kim, 2010). Progressive multifocal leukoencephalopathy, an infection caused by reactivation of the John Cunningham (JC) virus, has also been reported in RA patients treated with Rituximab (Fleischmann, 2009). Immuno suppression also can lead to a theoretical risk of malignancy, as tumor surveillance by the immune system may be affected (Kahlenberg and Fox, 2011). Since RA patients have an increased risk of lymphoma secondary to the disease itself, the extent of the increased risk of
Table 1: Adverse effects associated with various drugs.

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>COMPLICATION</th>
</tr>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>Pneumonitis, Mouth ulcers, Alopecia (Luo et al., 2013)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Retinal toxicity, Haemolytic anemia, skin discoloration Nausea, Diarrhea, Vomiting, Loss of appetite, Skin rash (Luo et al., 2013)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Gastrointestinal disorder, myelosuppression, rashes, Haemolytic anemia (Sun et al., 2013)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Adrenal suppression (Lis et al., 2014)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Tuberculosis, hepatic reactions, including acute liver failure, jaundice and hepatitis (Lis et al., 2014)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Multiple sclerosis, inflammation of spinal cord and optic nerves (Lis et al., 2014)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Hypersensitivity reactions, Anemia</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Pneumonia, fungal infection, tuberculosis, hepatitis B, malignancies (Brady et al., 2015)</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Peptic ulcer, cataract, muscle atrophy (Joseph et al., 2016)</td>
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Figure 1: Side effects exerted by commonly used synthetic drugs for RA.

Developing a cancer such as lymphoma while taking immunosuppressive medications remains debatable (Askling, 2008). The side effects exerted by these synthetic drugs for RA are illustrated in Figure 1. Therefore an extensive research on the formulation of herbal drug is under great attention. Many plants are already known for their potential anti-inflammatory activity but their molecular mechanism still remains unknown. Therefore, the review concentrates majorly on managing RA with herbal interventions.

HERBAL ALTERNATIVES FOR RA THERAPY

The main stream drugs for RA have various adverse effects and moreover some of the drugs are quite expensive. Owing to these limitations there is a need to revolutionize the RA therapy using natural products. Herbal products are the source of various bioactive components with therapeutic activity that could potentially be used for the development of new drugs. The structures of bioactive compounds which exert medicinal implication for RA prevention are illustrated in Figure 2. The aggressive role of inflammation which is associated with various diseased conditions needs to be reduced in order to prevent the inflammatory diseases. So to subdue this, different kind of safe and effective anti-inflammatory agents are available such as aspirin and other non-steroidal anti-inflammatory drugs. These anti-inflammatory agents are advantageous to cure the disease but they also possess certain severe side effect, costly and are effective on a limited proportion of RA patients (Dudics et al., 2018). Over the past years, herbal
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Figure 2: Structures of plant compound with medicinal implications found in the phytomedicines (Created with Chemsketch software).

Herbal medicines are used for the treatment of various diseases. According to WHO report, around 80% of world’s population counts on the traditionally known medicines (WHO 2002). These could be a potential alternative that could replace these synthetic drugs. Herbal medicines are reducing the risks of side effects and is also cost effective than the biological agents (Xia et al., 2020). Moreover, herbal products can control arthritic inflammation through various pathways, for example, inhibition of effectors molecules (e.g., pro-inflammatory cytokines and chemokines), induction of anti-inflammatory mediators (e.g., IL-4, IL-10), regulation of the Th17/Treg balance, and modulation of the osteo-immune cross-talk (Nanjundaiah et al., 2012; Astry et al., 2015; Venkatesha et al., 2016). This review summarizes some of the potential common herbs which were proved to be beneficial for reducing RA pathogenesis contributing minimal side effects. Mechanistic pathways of these herbal plants in inhibiting RA progression are also been discussed, focusing majorly on the reduction of inflammatory and other disease progressing molecules which directs toward detrimental symptoms of RA.

**Urtica dioica**

*Urtica dioica* L. is a perennial plant commonly known as stinging nettle belongs to the *Urticaceae* family. It is widely distributed throughout the temperate and tropical areas around the world, particularly in the Himalayas from Kashmir to Kumaon (Joshi et al., 2014). The plant has been known for its various pharmacological activities such as antioxidant, anti-inflammatory, anti-ulcer, anti-colicis, antiviral, anticancer, antibacterial, antimicrobial, antifungal, anti-androgenic, insecticide, immunomodulatory, hypo-cholesterolemic, hypoglycemic, anti-arrhythmic effects (Joshi et al., 2014). It shows anti-inflammatory effect by inhibiting activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) by interfering with its DNA binding activity (Joshi et al., 2014). A similar study has attributed the potential of *Urtica dioica* to inhibit the pro-inflammatory transcription factors by suppressing the activation of NF-κB (Riehman et al., 1999). Inhibition of the transcription factor NF-κB was demonstrated in different cell types including T-cells, macrophages, fibrosarcoma and epithelial cells. Inhibition was also demonstrated in response to several stimuli by stinging nettle leaf extracts as the extracts stabilize the inhibitor IκBα by preventing its proteolytic degradation (Riehman et al., 1999). Methanolic root extract of *Urtica dioica* was used in preparation of a herbal gel and was applied in a carrageenan-induced hind rat paw edema model. Approximately 55.05% inhibition of paw edema and 58.21% analgesia were observed after 24 hr compared
with a standard indomethacin gel. Moreover the herbal gel has been found to be safe as no skin irritation was observed in the model after primary skin irritation test. As a result this gel has been suggested to be used as an effective and safe treatment for rheumatoid arthritis and can be an alternative to NSAIDs (Liao et al., 2016). Therefore due to the potential to inhibit the pro-inflammatory transcription factors it can be an effective alternative therapy to treat RA.

**Strychnos potatorum**

*Strychnos potatorum* L. belongs to *Loganiaceae* family, also known as clearing nut tree (Yadav et al., 2014). It is commonly found in Sri Lanka, Burma and Central parts of India. It is a deciduous tree having height up to 12m. Traditionally it is used for the treatment of diseases like diabetes, chronic diarrhea, gonorrhea, bronchitis, leukorrhea, gastropathy, dysentery, renal and vesicle calculi, conjunctivitis, scleritis, ulcers and other eye diseases (Sanmuga Priya and Venkataraman, 2007). It also possesses anti-diabetic, anti-inflammatory, hepatoprotective, anti-oxidative and anti-ulcerogenic potential (Yadav et al., 2014). It inhibits Cyclooxygenase (COX) enzyme thereby inhibiting the production of prostaglandins (PG) on carrageenin induced inflammation in rats (Sanmuga Priya and Venkataraman, 2007). A significant decrease in rat paw edema and body weight were observed in Freund's complete adjuvant (FCA) induced arthritic rats upon treatment with *Strychnos potatorum* aqueous extract (SPE) and the *Strychnos potatorum* whole seed powder (SPP). These SPP and SPE treatment at the dose of 200 mg/kg/p.o recovers the hematological parameters like Hemoglobin (Hb), Red blood cell (RBC), White blood cells (WBC) and Erythrocyte sedimentation rate (ESR) and biochemical parameters (blood urea, serum creatinine, total proteins and acute phase proteins) in the arthritic rats (Ekambaram et al., 2010). Crude powder (SPP) and aqueous extract (SPE) of *S. potatorum Linn* were proved to be effective in antioxidant defense system against Freund's complete adjuvant (FCA) induced arthritis in rats at the dose of 200 mg/kg/p.o for 14 and 28 days and also induces in vitro antioxidant activity against Ferrous thiocyanate (FTC) and Thiobarbiturate (TBA) induced lipid peroxidation. Oxidative stress was significantly reduced in SPP and SPE treated arthritic rats compared to control arthritic rats as the drugs SPP and SPE have scavenged the free radicals by various antioxidant phytochemicals like steroids, triterpenes and polyphenolics present in it either by individual or by combined actions. Moreover it was observed that SPE has higher antioxidant activity compared to SPP (Ekambaram et al., 2011). Another study showed that the SPE and SPP normalized the lysosomal enzymes and glycoproteins and increased the altered collagen content in the Freunds adjuvant induced arthritic rats. It may be due to its membrane-stabilizing action and suppression of the collagenases that destroys collagen and bone (Ekambaram et al., 2011). Thus, it can be a potent alternative in the treatment of RA.

**Cinnamomum cassia**

*Cinnamomum cassia* of *Lauraceae* family is an ancient spice, commonly known as cinnamon (Bansode, 2012). Its cultivation is distributed in China, India, Vietnam, Indonesia and other countries. It exhibit anti-cancer, anti-ulcer, anti-inflammatory, heptoprotective, anti-microbial, anti-fungal and anti-HIV activity and are potent inhibitors of nitric oxide (NO) and cyclooxygenase (COX) (Bansode, 2012). The essential oil of cinnamon bark inhibits the synthesis of pro-inflammatory cytokines such as monocyte chemoattractant protein 1, Interferon gamma (IFN-γ), interferon inducible T-cell alpha chemoattractant and monokine induced by gamma interferon (MIG) (Han and Parker, 2017). Studies on the hydroalcoholic extract of *C. cassia* bark have shown significant reduction in swelling of joint as well as IL-1β and TNF-α level in Complete Freund's adjuvant (CFA) induced arthritis. TNF-α receptor expression was reported to get decreased in rats treated with Indomethacin or *C. cassia* hydroalcoholic extract (CCHE) (Sharma et al., 2018). A study demonstrated that cinnamaldehyde, cinnamic alcohol, cinnamic acid, and coumarin, the constituent of *C. cassia* inhibit the levels of NO, tumor necrosis factor (TNF-α), and prostaglandin E2 (PGE₂) in lipopolysaccharide (LPS)-stimulated mouse macrophage (RAW264.7) and carrageenan (Carr)-induced mouse paw edema model(Liao et al., 2012). Recent study by Liu et al. in 2020 reported that Cinnamaldehyde (CA), an essential component of *Cinnamomum cassia* have the potential to impart anti inflammatory effects against (RA). Moreover in-vitro studies proved that the expression of succinate receptor GPR91 was suppressed by CA followed by the inhibition of Hypoxia-inducible factor 1-alpha (HIF-1α) activity. The study also demonstrated that CA inhibited the expression of NLRP3, usually gets activated by HIF-1α leading to the inhibition of inflammasome (a multipeptide oligomer in the cytosol that activates the inflammatory response) assembly and IL-1β processing (Liu et al., 2020). These findings prove that *Cinnamomum cassia* can be a herbal alternative for RA.

**Allium sativum**

*Allium sativum* L. of *Liliaceae* family is commonly known as garlic, native to Asia but is also cultivated in Europe, China, Egypt and Mexico (Mikaili et al., 2013). Leaves and cloves of *A. sativum* are used as traditional medicines and are known for various therapeutic properties including
antibacterial, cardioprotective, antiviral, anti-parasitic, anti-inflammatory and anticancer (Mikaili et al., 2013). Presence of sulfur compound thiacremonone inhibits inflammation of nervous tissues and amyloidogenesis via inhibition of NF-κB activity (Mikaili et al., 2013). A. sativum have shown to inhibit the level of IL-17 cytokine without affecting cell proliferation in human peripheral blood mononuclear cells (PBMCs). Synovium and synovial cultures from RA patients contains increased levels of IL-17 (Moutia et al., 2016). A study conducted on female patients (n=70) suffering from RA supplemented with 1000 mg of garlic for 8 weeks resulted in improvement of clinical symptoms like fatigue, serum level of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and erythrocyte sedimentation rate (ESR) at the end of the study (Moosavian et al., 2020). Treatment of Aged garlic extract (AGE) with or without Methotrexate (MTX) in CIA models resulted in increased antioxidants, total glutathione and superoxide dismutase (SOD) and catalase (CAT) enzymes activities and decreased malondialdehyde (MDA) levels in comparison to only Collagen induced arthritis (CIA) and CIA-MTX treated groups. Simultaneously, there is a significant inhibition of cytokines (CRP and TNF) and interleukins (IL-17, IL-6, and IL-1) expression in AGE treated groups compared to control rats which supports the fact that Allium sativum has potent anti inflammation property and also diminishes hepatotoxicity when given in combination with MTX (Badr and Arafa, 2020).

Coriander sativum

Coriander sativum, an annual herb commonly known as coriander belongs to the Apiaceae family (Jinous, 2012). It is native to the Mediterranean but cultivated worldwide as a culinary herb. It is used as a herb, possesses antibacterial, anti-oxidant, anti-diabetic, hepatoprotective, anti-bacterial, and anti-fungal activities (Asgarpanah and Kazemivash, 2012). It significantly lowers the production of NO, Prostaglandon E2 (PGE2), inducible nitric oxide synthase (iNOS), cyclooxygenase-2, and pro-interleukin-1β expression, indicating to have a strong anti-inflammatory property by restraining NF-κB activation and Mitogen activated protein kinase (MAPK) signal transduction pathway in Lipopolysacharide (LPS)-induced macrophages(Wu et al., 2010). The hydroalcoholic extract of C. sativum (CHSE) was studied in adult wistar rats and the expression of TNF-R1, IL-1β and IL-6 in the synovium was observed to be down regulated (Nair et al., 2012). CSHE at a dose of 32 mg/kg causes significant reduction in paw edema and dry granuloma weight in carrageenan-induced paw edema model. Moreover there was a significant reduction of serum IL-6 and IL-1β levels and Tumor necrosis factor receptor 1 (TNF-R1) expression on peritoneal macrophages (Nair et al., 2012). Studies have been reported that the aqueous and ethanolic extracts of C. sativum seeds acts as an analgesic and provide anti-inflammatory activities in Carrageenan induced paw edema (Bhat et al., 2014).

Curcuma longa

Curcuma longa L. native to Southwest India, known as turmeric or Haldi commonly belongs to the Zingiberaceae family (Ashraf and Sultan, 2017). It is known for its wide spectrum of medicinal properties like anti-fungal properties, anti-inflammatory, hepatoprotective, anti-tumor, anti-viral, anti-depressant and anti-cancer activities, and is also used as a drug in Ayurvedic system (Ashraf and Sultan, 2017). It has the ability to inhibit inflammation by directly binding to TNF-α thereby suppressing its production and also decreases the production of various other interleukins by inhibiting NF-κB. Tsou et al. studies revealed the inhibition of NF-kB activation induced by Protein kinase B or AKT and IL-1β with curcumin, mediated by down-regulation of COX-2 and Matrix metalloproteinases (MMP-9) and reducing nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBa) phosphorylation in IL-1β- and TNF-α-stimulated human articular chondrocytes (Tsou et al., 2012). In case of RA, Lee et al. found that under in vitro conditions, a curcumin like compound diarylpentanoid 2, 6-bis (2, 5-dimethoxybenzylidene) cyclohexanone eradicated the p65 NF-kB nuclear translocation. Additionally it suppresses the binding activity of NF-kB DNA in the Phorbol 12-myristate 13-acetate (PMA) which is a direct activator of protein kinase C stimulated synovial fibroblasts through inhibition of COX-2, IL-6, MMP-3, collagenase and pro-gelatinase B (pro-MMP-9) (Lee et al., 2014). Study on patients (n=18) provided with 1200 mg/day of curcumin, showed significant improvement from baseline in morning stiffness, walking time and joint swelling (Deodar et al., 1980). Joint swelling was dramatically (90-100%) inhibited in female rats with streptococcal cell wall (SCW) induced arthritis by administering crude or refined turmeric essential oils (TEO) extracts (Funk et al., 2010). Significant mean difference in Erythrocyte sedimentation rate (ESR). Arthritic score (AS) and radiological scores were observed in (CIA) induced Sprague-Dawley rats after treatment with 110 mg/ml/kg CL compared to vehicle treated group (Anna et al., 2011). Induction of apoptosis and growth inhibition, suppression of anti-apoptotic Bcl-2 and X-linked inhibitor of the apoptosis protein, increase of pro-apoptotic Bax expression were observed in synovial fibroblasts of RA patients when they were treated with curcumin, a polyphenolic compound from the rhizome of Curcuma longa. Moreover the occurrence of proteolytic activation of caspase-3 and caspase-9, and the concomitant degradation of poly(ADP-ribose) polymerase protein, decrease in the expression levels of the COX-2 were
also reported which demonstrated the therapeutic potential of *C. longa* against hyperplasia of the synovial fibroblasts in RA (Park et al., 2007).

**Zingiber officinale**

*Zingiber officinale*, a species commonly known as ginger belongs to *Zingiberaceae* family (Dhanik et al., 2017). It is widely used in Chinese, Arabian, Caribbean and Ayurveda medicine systems. It is known for its anti-oxidant, antimicrobial, anti-cancer, anti-diabetic, analgesic, anti-pyretic, anti-inflammatory and anti-platelet aggregating activities (Dhanik et al., 2017). Gingerol, shogaol, and other structurally-related substances present in *Z. officinale* commonly known as ginger inhibits the biosynthesis of prostaglandin and leukotriene by suppressing 5-lipoxygenase or prostaglandin synthetase. They also down regulate the production of pro-inflammatory cytokines (IL-1, TNF-α, and IL-8). Another study by Pan et al. (2008) reported the potential of shogaol to reduce levels of inflammatory inducible nitric oxide synthase (iNOS) and COX-2 gene expression (Pan et al., 2008). Jung et al. (2009) indicated that rhizome hexane fraction extract of *Z. officinale* hampers the over production of NO, PGE₂, TNF-α, and IL-1β (Jung et al., 2009). The alcoholic and aqueous extract of rhizome of *Z. officinale* have shown significant anti arthritic activity against form aldehyde induced arthritis in rats but the pathway still remains unclear (Prakash and Katiyar, 2016). Inhibition of joint swelling in streptococcal cell wall-induced arthritis model by both crude dichloromethane ginger extract and fractions containing only gingerol and their derivatives was reported in the study by Funk et al. (2009), however the crude extract was found to be more effective (Funk et al., 2009). Another study by Funk et al. in 2016 showed the anti-inflammatory effects of other secondary metabolites of ginger, the essential oils, which contain terpenes and is reported to have phytoestrogenic activity in female Lewis rats with SCW-induced arthritis (Funk et al., 2016). Fouda and Berika, (2009) reported the anti-inflammatory potential of *Zingiber officinale* rhizomes with doses more than 50 mg/kg/day in CIA rat model by demonstrating the amelioration of disease incidence, clinical scores, joint swelling, destruction of cartilage and also reduction of cytokines like IL1β, IL-6, TNF-α and anti CII (collagen type II) antibodies (Fouda and Berika, 2009). *Zingiber officinale* can be an advantageous herbal option in the treatment of RA.

**Emblica officinalis**

*Emblica officinalis* of *Euphorbeceae* family is also known as the Indian gooseberry or Amla (Khan, 2009). It is native to India, also growing in Sri Lanka, Uzbekistan, South East Asia, and China. Various preclinical studies have manifested the cardioprotective, antipyretic, wound healing, analgesic, anti-tussive, anti-diarrheal, anti-atherogenic, adaptogenic, gastroprotective, anti-anemic, hepatoprotective, anti-hypercholesterolemic, anti-atherosclerotic, nephroprotective, and neuroprotective potential of *E. officinalis* (Khan, 2009). It significantly lowered the expression of pro-inflammatory cytokines IL-6, TNF-α and suppresses the phosphorylation of NF-κB in rats (Malik et al., 2016). *E. officinalis* fruits have the potential to trigger programmed cell death of human primary osteoclasts that are involved in the pathogenesis of RA (Penolazzi et al., 2008). A study from Golechha et al. (2014) reported the management of acute and chronic inflammation in rats with hydroalcoholic extract of *Emblica officinalis* (HAEEO) (Golechha et al., 2014). Finding the potential of *Emblica officinalis*, can be drawn as a beneficial anti-inflammatory, anti-microbial, antitumor, anti-viral, anti-diabetic, anti-oxidant and anti-malarial properties (Febrina et al., 2018). α-Mangostin compound present in *G. mangostana* lowers the expression level of TNF-α, MCP-1, and IL-6 (Kim et al., 2017). Peel extract of *G. mangostana* studied by Wahyu et al exhibited the inhibition of COX-2, IL-6, IL-1β, and NO by *G. mangostana* peel extract (GMPE) and its components α-mangostin, and yamangostin in LPS-induced RAW264.7 cells along with regulating the activation of macrophages (Widorwati et al., 2016). A study reported that mangosteen and its ingredients inhibited the secretion of TNF-α from cells with IC50 range from 2 μg/ml to 11 μg/ml. It also inhibited the secretion of TNF-α and IL-6 in LPS-stimulated mice with ED50 (median effective dose) less than 100 mg/kg (Lee et al., 2013). Zhu et al. (2018) showed the effect of *G. mangostana* pericarp ethanol extract in CIA rats and reported a significant reduction in anti-cyclic citrullinated peptide antibody, IL-17 and TLR4 expression in CIA rats along with increase in FOXP3, CD25 mRNA expression (Zuo et al., 2018). A study by Fu et al. (2014) first reported the immuno suppressing action of isogarcinol, a natural compound extracted from *Garcinia mangostana* L. Oral administration of isogarcinol on CIA showed significant decrease in clinical scores, cytokines level in serum like IL-2 diminishing cartilage and bone erosion. This study also reported the decrease of iNOS, COX-2 mRNA expression, COX-2 mRNA expression, activity of NFAT (Nuclear factor of activated T-cells) and NF-κB expression (Fu et al, 2014) demonstrating its effectiveness to decrease the progression RA. It may therefore be considered for a phytomedicine for RA.

**Garcinia mangostana**

*Garcinia mangostana* L. of family *Clusiaceae* is a type of fruit native to Southeast Asia region (Febrina et al., 2018). It is commonly known as mangosteen and known for its beneficial anti-inflammatory, anti-microbial, antitumor, anti-viral, anti-diabetic, anti-oxidant and anti-malarial properties (Febrina et al., 2018). α-Mangostin compound present in *G. mangostana* lowers the expression level of TNF-α, MCP-1, and IL-6 (Kim et al., 2017). Peel extract of *G. mangostana* studied by Wahyu et al exhibited the inhibition of COX-2, IL-6, IL-1β, and NO by *G. mangostana* peel extract (GMPE) and its components α-mangostin, and yamangostin in LPS-induced RAW264.7 cells along with regulating the activation of macrophages (Widorwati et al., 2016). A study reported that mangosteen and its ingredients inhibited the secretion of TNF-α from cells with IC50 range from 2 μg/ml to 11 μg/ml. It also inhibited the secretion of TNF-α and IL-6 in LPS-stimulated mice with ED50 (median effective dose) less than 100 mg/kg (Lee et al., 2013). Zhu et al. (2018) showed the effect of *G. mangostana* pericarp ethanol extract in CIA rats and reported a significant reduction in anti-cyclic citrullinated peptide antibody, IL-17 and TLR4 expression in CIA rats along with increase in FOXP3, CD25 mRNA expression and IL-10 secretion (Zuo et al., 2018). A study by Fu et al. (2014) first reported the immuno suppressing action of isogarcinol, a natural compound extracted from *Garcinia mangostana* L. Oral administration of isogarcinol on CIA showed significant decrease in clinical scores, cytokines level in serum like IL-2 diminishing cartilage and bone erosion. This study also reported the decrease of iNOS, COX-2 mRNA expression, COX-2 mRNA expression, activity of NFAT (Nuclear factor of activated T-cells) and NF-κB expression (Fu et al, 2014) demonstrating its effectiveness to decrease the progression RA. It may therefore be considered for a phytomedicine for RA.
Psidium guajava

Psidium guajava, the common fruit guava belongs to Myrtaceae family, majorly found in the tropical and temperate regions (Gutiérrez et al., 2008). It is known to show the following pharmacological properties like antioxidant, hepatoprotection, anti-allergy, anti-microbial, anti-genotoxic, anti-plasmodial, cytotoxic, anti-spasmodic, cardioactive, anti-cough, anti-diabetic, anti-inflammatory and anti-nociceptive activities (Gutiérrez et al., 2008). It is known to reduce the levels of iNOS and COX-2 at the transcription level (Jang et al., 2014). It also suppresses extracellular signal-regulated kinases ERK1/2 of MAPK pathway thereby acting as an anti-inflammatory agent (Jang et al., 2014). Studies have demonstrated the inhibition of carrageenan-induced paw edema when treated with the ethanolic extract of P. guajava (Dutta and Das, 2010). Similar study was carried out in CFA induced arthritic rats upon treatment with ethanolic extract of P. guajava, a significant suppression of paw swelling and arthritic score with a dose of 250 mg/kg was observed. Repair of knee joint, knee joint synovial membrane and cartilage has also been reported (Baroroh et al., 2016). Another study reported the anti-arthritic effect of hydroalcoholic extract of Psidium guajava Linn. in complete Freund’s adjuvant induced arthritic rats (Jahagirdar et al., 2010). The studies therefore exhibit the efficacy of P. guajava in the management of RA.

Moringa oleifera

Native to India, Moringa oleifera commonly known as drumstick tree belongs to the Moringaceae family (Gopalkrishnan et al., 2016). It has high nutritional as well as therapeutic values. It exhibits anti-diabetic, anti-microbial, anti-cancer and anti-inflammatory activities (Gopalkrishnan et al., 2016). Earlier study reported that the ethanolic extract of Moringa leaves exhibits strong inhibition against inflammatory paw edema and decreases the arthritic index (Mahdi et al., 2018). Similar study reported that the hydroethanolic leaves extract of M. oleifera significantly suppressed the protein expression of inflammatory markers like cyclooxygenase-2, and nuclear factor kappa-light-chain-enhancer of activated B-cells p65 in LPS-induced RAW264.7 macrophages in a dose-dependent manner (Fard et al., 2015). In 2007, a study by Mahajan et al. (2007) in female wistar rats with adjuvant induced arthritis upon treatment with ethanolic extract of seeds of Moringa oleifera Lam. showed a significant reduction in RF, TNF-α, IL-1, and IL-6 expression level in serum, paw edema volume and arthritic index score and also caused an alteration in oxidative stress (Mahajan et al., 2007). Methanolic extract of Moringa oleifera also showed anti-arthritic activity against turpentine oil, formaldehyde and CFA induced arthritis which proves that M. oleifera has the potential to be a potant phytomedicine for RA (Kumar et al., 2013).

Periploca forrestii

Periploca forrestii belongs to the Apocynaceae family and is widely used in Chinese medicine system (Dong et al., 2017). It is known for its anti-inflammatory and immunosuppressive potential. Ethanolic extract of P. forrestii potentially inhibits the LPS-stimulated production of NO, PGE2 and cytokines like TNF-α, IL-6 and IL-10. It also suppresses the phosphorylation and degradation of inhibitor of NF-κB-α and the signaling pathway MAPK. The anti-arthritic effect of the cardenolide-rich and caffeoylquinic acid-rich fractions (CDLFs and CQAFs) of P. forrestii was studied in CIA rats. The results showed that CDLF and CQAF could suppress the paw swelling in CIA rats and reduced the levels of RF, TNF-α, IL-6, IL-1β, PGE2, NO, and MDA (Ting et al., 2018). Another study demonstrated the potential of Periplocin (an active compound of Periploca forrestii) to suppress pro-inflammatory cytokines levels of IL-6, IFN-γ, TGF-β1, IL-13 and IL-22 and transcription factor levels of T-bet, GATA3, and C-Jun genes in adjuvant-induced arthritis (AIA) rats (Liu et al., 2016). In a study by Huang et al. (2012), it was shown that there was a significant reduction in paw swelling and in the expression level of IL-1β, IL-6 and TNF-α in the serum and inflammatory tissue of AIA rats treated with P. forrestii extract compared to controls (Ming-jin et al., 2011). Moreover ethanol extract of P. forrestii was also proved to inhibit COX2 and PGE2 expression and restrained proliferation of rheumatoid arthritis synovial fibroblasts (RASF) at a concentration of 250 and 500 mg/ml (Jiang et al., 2015). Therefore it could be a favorable choice in treating RA.

Anoectochilus roxburghii

Anoectochilus roxburghii belongs to Orchidaceae family and is known as Jinxianlian in Chinese (Ye et al., 2017). The Chinese herb, also called the "king medicine" known for anti-oxidant activity, anti-lipemic, anti-inflammatory, anti-viral, liver protective, renal protective, immune-modulatory, sedative, and anti-neoplastic effects (Ye et al., 2017). It also lowers the cytokine level and the production of NO (Guo et al., 2019). Study by Guo et al. (2019) demonstrated that A.roxburghii polysaccharides (ARP) significantly suppress the production of NO, down-regulating the mRNA expressions of IL-1β and IL-6 and also phosphorylated iκB and p65 resulting in inhibition of nuclear factor κB (NF-κB) pathway in
Table 2: The bioactive components present in the herbal products and their target.

<table>
<thead>
<tr>
<th>ACTIVE COMPONENT</th>
<th>PLANT SOURCE</th>
<th>TARGET</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>Allium cepa (onions)</td>
<td>NF-κB, COX-2, TNF-α, 5LOX, TNF-α, IL-1β, AMs, RANKL</td>
<td>(Oliveira et al., 2014)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcuma longa</td>
<td>NF-κB, TNF-α, AMs, MMP-9, TL9, IL-6, IL-8, COX2, LOX</td>
<td>(Shakibaei et al., 2007)</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Veratrum grandiflorum</td>
<td>JNK, NF-κB, TNF-α, 5LOX, AMs, COX2, PGE2, MMP13</td>
<td>(Elmali et al., 2007)</td>
</tr>
<tr>
<td>8-methoxy-7,3′,4′-trihydroxyflavone</td>
<td>Albizia myriophylla</td>
<td>NO</td>
<td>(Bakasatae et al., 2018)</td>
</tr>
<tr>
<td>Myristicin</td>
<td>Trachydium roylei</td>
<td>IL-6, IL-1β, TNF-α, NO, PGE2</td>
<td>(Wang et al., 2016)</td>
</tr>
<tr>
<td>Guggulosteroine</td>
<td>Commiphora mukul</td>
<td>IFN-γ, IL-12, IL-1β, NO, NF-κB, COX-2</td>
<td>(Manjula et al., 2006)</td>
</tr>
<tr>
<td>Shagoal</td>
<td>Zingiber officinale</td>
<td>IL-1β, IL-6, TNF-α, INF-γ, NO, PGE2</td>
<td>(Naderi et al., 2015)</td>
</tr>
<tr>
<td>Cinnamic acid, Cinnamic alcohol,</td>
<td>Cinnamomum cassia</td>
<td>NO, TNF-α, PGE2</td>
<td>(Liao et al., 2012)</td>
</tr>
<tr>
<td>Cinnamic aldehyde, Cinnamic acid, &amp; Coumarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-linolenic acid (ALA)</td>
<td>Actinidia polygama</td>
<td>iNOS, COX-2, TNF-α</td>
<td>(Ren and Chung, 2007)</td>
</tr>
<tr>
<td>α-Mangostin</td>
<td>Garcinia mangostana</td>
<td>IL-6, TNF-α, MCP-1</td>
<td>(Kim et al., 2017)</td>
</tr>
<tr>
<td>Tetrandrine</td>
<td>Stephania tetrandra</td>
<td>TNF-α, IL-1β, IL-6, COX-2</td>
<td>(Li et al., 2018)</td>
</tr>
<tr>
<td>Thiacremonone</td>
<td>Allium sativum</td>
<td>NF-κB</td>
<td>(Mikaili et al., 2013)</td>
</tr>
</tbody>
</table>

Lipopolysacharide(LPS)-stimulated RAW 264.7 cells (Guo et al., 2019). It can be beneficial in halting the symptoms of RA.

**Tripterygium wilfordii**

*Tripterygium wilfordii* of the family Celastraceae is a Chinese herb (Di et al., 2008), used for the treatment of various autoimmune disorders and have potential antitumor, immune modulating and anti-inflammatory ability. It is also known as thunder god vine (Di et al., 2008). It reduces the expression NF-κB gene and accumulation of NO in cultured RAW 267.4 macrophages (Wang et al., 2016). Studies conducted by Bao et al. (2011) demonstrated that the extract of *T. wilfordii* inhibits the production of IL-2, TNF-α, IFN-γ, iNOS and COX-2. It also suppressed the secretion of MMP by synovial fibroblast and chondrocytes in CIA rats (Bao et al., 2011). Another study was reported on patients (n=70) who did not responded to NSAIDs for at least 2 months were administered with TWH (*Tripterygium wilfordii* Hook F), 60 mg/day or identically appearing placebo tablets for 3 months (Tao et al., 1989). At the completion of treatment, patients treated with TWH indicated significant improvement in joint tenderness score, swelling count, morning stiffness and grip strength. Another clinical trial by Tao et al. (2001) showed that ethyl acetate extract of *T. wilfordii* dosage up to 570 mg/day are safe and doses more than 360 mg/day are beneficial for RA patients (Tao et al., 2001). More clinical studies carried out by the same group in the year 2002 on RA patients, *Tripterygium wilfordii* proved to be beneficial in a study (Tao et al., 2002). Lv et al. (2015) showed through a clinical trial that *T. wilfordii* hook F (TWHF) monotherapy as well as TWHF plus methotrexate therapy was much better than methotrexate alone for RA patients (Lv et al., 2015). Some of the known bioactive components of herbal products are listed in Table 2 and represented in Figure 2.

**CONCLUSION**

RA associated with inflammation of multiple joints that ranges from pain to deformity presents hassles in diagnosis, often observed flare ups, polycyclical nature of RA progression and inconsistent response to therapies. Activation of several interrelated immune pathways and an imbalance in the cytokine networks significantly contributes to RA pathogenesis and inflammatory response. The available treatment includes non-steroidal anti-inflammatory drugs (NSAID’s) and steroids; these can manage the disease to a certain degree. These conventional treatments are associated with certain limitation including...
the cost, safety and the long term efficacy. Herbal medicines could be a promising and effective treatment for curing diseases like RA. Naturally available medicinal plants could be an economically feasible treatment and an alternative to the commercially available therapy. This review expressed strong evidences showing that the different extracts of these medicinal plants are potential enough to be established into certain agents that would possibly act as the prevention or treatment of RA. Moreover this review will provide the traditional folk knowledge and the discovery of potential compounds having promising pharmacological characteristics which can be useful to sustain the remission of RA. The poor bioavailability of the herbal products imposes a significant obstacle. In order to overcome this issue, researchers are looking for nano-particle delivery mechanism of such products and reported successful application of these methodologies. Nano-particles delivery system improves the pharmacological and therapeutic properties of the drug. Moreover, they can protect the drug against intracellular degradation and can efficiently deliver the drug to a specific target. In consequence, lower dose of the drug is required to achieve the desired efficacy. Thus, nanoparticles can also ensure controlled release of drug dosage and reduction in toxicity (Dudics et al, 2018). However, further research is mandatory for identification, isolation, characterization of the bioactive component from crude plant extracts, investigating herb-target interactions, its bioefficacy and safety aspects of these phytochemical agents for finding and developing novel natural drugs. Apart from this, global compliance of legislation is needed for mass production and marketing of herbal medicines which would be beneficial for the treatment of disease.

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