Chapter 2

Review of literature

2.1 TREATMENT OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis is one of the common chronic, systemic, inflammatory autoimmune disorders, in which immune system promotes inflammation in synovial damage and destruction of bone. It affects approximately 1% of general population worldwide, advance disease stages, reduces life expectancy, increases mortality and eventually results in large medical costs. Over recent years, rheumatoid arthritis is managed by conventional medicines like non-steroidal anti-inflammatory drugs (NSAIDs), steroids and disease modifying anti-rheumatic drugs (DMARDs). These medications are primarily directed towards the minimizing nociceptive pain, inflammation, preventing joint deformity and reduce the progression of cartilage and bone destruction (Rakesh, 2012).

However, unfortunately this therapeutics provide only symptomatic relief from pain and their prolonged usage display severe adverse effects such as gastrointestinal lesions, cardiovascular risks and reproductive toxicity. Therefore, treating this chronic disease with appropriate medication has led to a paradigm shift towards complementary and alternative medicine (CAM) (Ahmed et al., 2005). Due to the chronic nature of disease, many patients are likely to seek complementary options coping with this debilitating disease. CAM embraces 100 forms of treatment together. Among all therapies herbal medicines (phytotherapy) with diverse therapeutic effects are traditionally used for arthritis. Recent investigations have estimated that 60-90% of RA patients are likely to use plant derived anti-RA drugs with low cost, toxicity and high efficacy and due to the dissatisfaction of conventional medications used for RA (Pugh, 2003). Herbal medicine acts as a root for various traditional medicines such as Chinese medicinal system, Indian medicinal system and Amazonian ethnomedicine, which relies on herbs for preserving health (Soeken et al., 2003).
2.2 HERBAL MEDICATIONS COMMONLY USED IN THE PRACTICE OF RHEUMATOLOGY

2.2.1 *TRIPTERYGIUM WILFORDII* HOOK F

*Tripterygium wilfordii* Hook F (TwHF) that belongs to Celastraceae family is a perennial vine-like plant that grows in southern China and Taiwan commonly called Thunder God Vine. TwHF is a Chinese traditional medicine that has been used to treat various autoimmune and inflammatory disorders including RA, psoriasis, nephritis, ankylosing spondylitis, psoriasis, systemic lupus erythematosus and asthma for several centuries (Tao and Lipsky, 2000). The therapeutic effects of this extract are thought to be due to the presence of active principles like triptolide and tripdiolide. Both these compounds are found to possess immunosuppressive and anti-inflammatory properties. TwHF inhibits the production of inflammatory cytokines and mediators by transcriptional blocking of pro-inflammatory genes including interferon-γ, TNF-α, iNOS, COX-2 and IL-2 (Sylvester et al., 2001). The prophylactic treatment of TwHF showed considerable reduction of adhesion molecules such as ICAM-1, E-selectin and vascular cellular adhesion molecule-1 (VCAM1) mostly expressed by activated neutrophils, endothelial cells and synovial fibroblasts. In animal studies, triptolide has inhibited the disease progression of CIA in mice and rats by suppression of iNOS gene expression by downregulating the JNK and DNA binding activity of NF-κB pathway (Tao et al., 2002). Additionally, the active constituents of TwHF triptolide were shown to inhibit the LPS-induced cytokine production of COX-2, iNOS, IL-17, and other proteases like aggrecanase in human articular chondrocytes (Qui and Kao, 2003). A prospective, double blind, placebo-controlled trial study has shown therapeutic benefit in TwHF extract treated RA patients (360 mg/day for 20 weeks) when compared with placebo. The TwHF extract treated RA patients showed significant reduction in the number of tender and swollen joints and improvement in ESR and CRP level (Cibere et al., 2003).

2.2.2 *ZINGIBER OFFICINALE* (GINGER)

*Zingiber officinale*, the rhizome belongs to the Zingiberaceae family. Ginger is one of the common dietary constituents worldwide, and it is known to possess anti-
inflammatory, antioxidant, antiseptic and carminative properties. Ginger has its history of usage in Ayurvedic and Sino-Japanese medicine as therapeutic for treating inflammation and rheumatism. In addition, it is also being used for nausea, vomiting of pregnancy and dizziness. Z. officinale is reported to contain active principle including beta-carotene, caffeic acid, gingerols, linoleic acid and trace elements such as magnesium, phosphorus and potassium (Afzal et al., 2001). [6]-gingerol, the pungent phenolic constituent of ginger has shown to inhibit the LPS-induced NO production by down regulating the iNOS gene expression in macrophages and blocks the peroxynitrite-induced oxidation and nitration reactions in vitro (Jolad et al., 2004). Besides, ginger extract has shown to inhibit the generation of TNF-α pro-inflammatory cytokine expression in human synoviocytes and chondrocytes of osteoarthritis individual. Furthermore, an in vitro study has exhibited that gingerol derivatives were excellent inhibitors of PGE₂ and TNF-α and COX-2 expression in human synoviocytes by down regulating the activation of transcription factor NF-κB and degradation of its inhibitor IκB-α (Ippoushi et al., 2003). A randomized, double-blind, placebo-controlled trial study on ginger treated osteoarthritis patients has reported 60-70% of the individuals experienced reduction in joint pain versus placebo group (Bliddal et al., 2000). This beneficial effect of ginger could be attributed to its ability to inhibit the production of PGE₂ by blocking the COX and LOX mediated pathways in affected joints (Altman and Marcussen, 2001)

2.2.3 CAMELLIA SINENSIS (GREEN TEA)

Green tea is one of the commonly consumed beverages worldwide. The pharmacological property of green tea is attributed due to the presence of polyphenols known as catechins mainly epigallocatechin-3-gallate (EGCG) (Manning and Roberts, 2003). EGCG has been shown to be more potent antioxidant than vitamin C. EGCG plays a vital role in cartilage/chondrocytes protection (Rasheed et al., 2009). Singh and his colleagues (2002) reported that EGCG selectively inhibited the p46 isoform of c-jun-N-terminal kinase and other signaling pathways induced by IL-1β that resulted in reduced DNA binding activity of phosphorylated c-Jun and activation protein-1, and inhibition of inflammatory response in OA chondrocytes mediated by activating protein-1 (AP-1) (Siddiqui et al., 2004). In another study, pre-treatment of EGCG with cultured human OA
chondrocytes significantly inhibited the degradation of human cartilage proteoglycan and type II collagen by selective inhibition of IL-1β induced MMP-1 and MMP-13 and other matrix proteoglycans (Ahmed et al., 2002). In order to further support the chondroprotective effects of EGCG in arthritis, a recent study showed that collagen pre-incubated with EGCG proved a remarkable resistance against degradation by bacterial collagenase and MMP-1 (Goo et al., 2003). Furthermore, a circular dichroism spectral analysis revealed that EGCG treated collagen showed a higher free-radical scavenging activity than untreated collagen. Prophylactic administration of green tea has ameliorated the disease progression of inflammatory polyarthritis in collagen type II-induced arthritis (CIA) in mice (Bae et al., 2009). Further animal studies proved that availability of total immunoglobulins (IgG) and type II collagen-specific IgG levels were found to be reduced in green tea administered rats compared to that of control rats. The biochemical and histopathology results also correlated with above findings with marked reduction of inflammation in synovium (Ahmed et al., 2002). With global availability of green tea, low toxicity, and its low cost are strong enough to advocate for its usage as conventional medicine for both RA and OA.

2.2.4 CURCUMA LONGA (TURMERIC)

Turmeric is commonly used as a yellow coloring and flavoring agent from the root of Curcuma longa, a member of Zingaberae family. It is usually used as a spice for centuries in Indian subcontinent. Curcumin present in turmeric has been well documented as anti-inflammatory agent and also used for various other medicinal conditions including common cold, skin infections, wound healing, liver and urinary tract and as a ‘blood purifier’ in ayurvedic medical system (Mukhopadhyay et al., 1982). Curcumin is the major active principle present in turmeric, which comprises up to 90% of total curcuminoid content. Likewise it also contains demethoxycurcumin and bis-demethoxycurcumin as other active principles. In animal studies, curcumin has shown to decrease carrageenan-induced paw edema in rats and mice and reduce the level of inflammatory glycoprotein, Gp A72 (Srivastava et al., 1995). Several lines of evidence have reported that curcumin inhibits/modulates upstream pathways of JNK, AP-1 and NF-κB, thus leading to down regulation of the expression of TNF-α, IL-1β, MMPs, and
COX (Schulze et al., 2004). This polyphenol has also shown to suppress the expression of matrix MMP-3 and MMP-9 by inhibiting the NF-κB and JNK pathway (Joe et al., 1997). Curcumin antagonizes the effects of IL-1β induced degradation of extracellular matrix such as collagenase and stromelysin, involved in the pathogenesis of RA. A double blinded crossover clinical trial reported that RA patients treated with curcumin (1200 mg/day) and phenylbutazone (300 mg/day) over a duration of 2-weeks showed significant improved response in terms of joint swelling, morning stiffness and walking time (Deodhar et al., 1980).

2.2.5 GAMMA-LINOLENIC ACID

Gamma-linolenic acid (GLA) is an unsaturated fatty acid found in oils of evening primrose (Oenotherabiennis), black currant seed (Ribes nigrum) and borage seed (Borago officinalis). It is believed to be effective in reducing the inflammation in patients with rheumatoid arthritis (RA) and Sjogren’s syndrome. During metabolism, GLA is converted to dihomogammalinolenic acid (DGLA), the immediate precursor of prostaglandin E₁ (PGE₁), an eicosanoid, which is well known for its anti-inflammatory and immunoregulatory properties. Besides, GLA forms 15-hydroxyl derivative and blocks the transformation of arachidonic acid to leukotrienes (LTs). Thus by increasing the GLA intake as dietary supplement acts as a competitive inhibitor of PGE₂ and LTs and thus suppresses inflammation. Further in vitro studies reveal that administration of GLA suppresses the LPS-induced pro-IL-1 mRNA gene expression modestly and IL-1β induced auto-induction of inflammatory response in patients with chronic inflammatory diseases (Belch and Hill, 2000)

2.2.6 OTHERS

Perna canaliculus (Perna), is a New Zealand green-lipped mussel, it is a part of traditional diet of the Maori inhabitants of New Zealand. Perna has shown potent anti-inflammatory properties, which are comparable to that of non-steroidal anti-inflammatory drugs (NSAIDs) (Cobb and Ernst, 2006). A study on animal model demonstrated the anti-arthritic effect of Perna that is attributed due to the presence of omega-3 poly unsaturated fatty acids, which inhibits the biosynthesis of prostaglandins (PGE₂) from
arachidonic acid metabolism through COX pathways (Miller and Wu, 1984). In addition, another animal study demonstrated that Perna reduced the production of pro-inflammatory mediators, anti-collagen antibody and superoxide levels release (Lawson et al., 2007). Unlike NSAIDs, Perna has proved efficacy in selective blocking of COX-2 enzyme and offers potential gastrointestinal protection to ulcer-prone patients (Ulbricht et al., 2009).

Thus, plant derived products offer more advantages that surpass the shortcomings of conventional therapeutics. This encourages further study and rigorous experimenting for the development of better treatment modalities for inflammatory joint diseases and other degenerative diseases.

2.3 TRIPHALA

As described earlier, triphala is a commonly used Ayurvedic herbal compound derived from fruits of three trees, e.g., Indian gooseberry (Emblica officinalis Gaertn, family Euphobiaceae), Belleric myrobalan (Terminalia bellerica Linn, family Combretaceae), and Chebulic myrobalan (Terminalia chebula Retzr, Combretaceae) (Sandhya et al., 2006). This compound, rich in anti-oxidants, plays an essential role in the treatment of a wide variety of conditions like infection, obesity, anemia, fatigue, constipation, and in infectious diseases like tuberculosis, pneumonia, and AIDS (El-Mekkawy et al., 1995). Triphala has been shown to be a rich source of Vitamin C, ellagic, gallic, and chebulinic acids, bellericanin, β-sitosterol and flavanoids (Jagetia et al., 2002). Investigations have shown that triphala imparted biological effects, including acting like an anti-oxidant (Takagi and Sanashiro, 1996), anti-tumor (Kaur et al., 2005), anti-diabetic (Sabu and Kuttan, 2002), anti-proliferative, anti-mutagenic (Kaur et al., 2002), and radio-protective (Jagetia et al., 2002) agent. Our preliminary studies with triphala have demonstrated the anti-inflammatory, immunomodulatory, and lysosomal membrane-stabilizing effects in arthritic animal models (Rasool and Sabina, 2007; Sabina et al., 2009; Kalaiselvan and Rasool, 2015a,b).
2.3.1 DESCRIPTION OF INDIVIDUAL INGREDIENTS OF TRIPHALA

2.3.1.1 TERMINALIA CHEBULA

Terminalia Chebula has extensively been used in ayurveda, siddha, unani, and homeopathy, traditional medicinal systems of India. It has become a cynosure of modern medicine. Terminalia chebula (T. chebula) Retz belongs to the family of combretaceae. It is known as Chebulic myrobalan in English, harad and harra in Hindi, katukka in Malayalam, halela in Urdu and kadukkai in Tamil. It is abundantly found all throughout India especially in deciduous forests and areas of light rainfall. It grows at the altitude of 2000 to 6000 m in clayey and shady soils and attains the height up to 30 m. It is a popular folk medicine possessing diverse health benefits and has been used as traditional medicine for household remedy against various human ailments since antiquity, antitussive, diuretic and sepsis. It also increases the frequency of stools by evacuating the bowel completely (Mammen et al., 2012). It falls under rasayana group of medicine in ayurvedic texts where it aids in balancing Vata, one of the tridoshas. Terminalia consists of at least 250 different species distributed worldwide. Among these, at least seven Terminalia species like vijaya, rohini, putana, amrita, abhaya, jivanti and chetaki were traditionally used for various ailments. (Chattopadhyay et al., 2007)

2.3.1.2 PHYTOCONSTITUENTS OF TERMINALIA CHEBULA

Fruits of Terminalia chebula are evidenced to possess 32-42% tannins and this content varies according to the geographical distribution. The tannins of T. chebula contains pyrogallol (hydrolysable) type which is found to be of 14 of hydrolysable tannin components like punicalagin, chebulic acid, gallic acid, chebulanin, corilagin, neochebulinic, ellagic acid, chebulegic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl-β-D-glucose, 1,6-di-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin. Other constituents include phenolics such as chebulinic acid (30%), ellagic acid and anthraquinones (Kumar et al., 2009). Besides it also has minor constituents of phenolic compounds such as corilagin, galloyl glucose, punicalagin, terflavin A, and maslinic acid. In addition, Triterpenoid glycosides such as chebulosides I and II, arjunin, arjunglucoside, 2α- hydroxyursolic acid and 2α-hydroxymicromiric acids were isolated
from the fruit of *T. chebula*. Further, flavonol, glycosides, triterpenoids, coumarin conjugated with gallic acids called chebulin were also reported (Jayaramkumar, 2006). Furthermore, the leaves were found to contain polyphenols such as punicalin, punicalagin, terflavins B, C, and D. The plant is found to contain phloroglucinol and pyrogallol, along with phenolic acids such as ferulic, p-coumaric, caffeic and vanillic acids. Other components include fructose, amino acids, succinic acid; betasitosterol, resin and the purgative principle of anthraquinone are also present. It also consists of nutrients such as vitamin c, protein, amino acids and minerals (Rangsriwong *et al*., 2009).

### 2.3.1.3 EMBLICA OFFICINALIS

*Emblica officinalis* (EO) enjoys a hallowed position in Ayurveda. The vernacular names include Emblicmyrobalan or Indian Gooseberry in English, amla in Hindi, amloki in Bengali, nelli and amlakam in Malayalam and nelli and nellikai in Tamil. The fruits of EO widely used in Ayurveda have a beneficial role in wide range of disease. Abundantly found in the mixed deciduous forests of India ascending to 1500 m on the hills, it is cultivated in gardens and homeyards. Fruit is three chambered, pale-green, 1.5 to 2.5 cm in diameter, fleshy edible mesocarp and stony endocarp. It is one of the well-known rasayanas in Ayurveda for its anti-oxidant and anti-aging properties. It possesses a protection against various diseases like cancer, diabetes, liver treatment, heart trouble, ulcer and anemia (Khan, 2009). In a recent review article, the fruit of *Phyllanthus emblica* has been described to possess numerous pharmacological activities, such as gastroprotective, antiulcerogenic, hypolipidemic, and anti-diabetic activities. Likewise, it has a beneficial, role and has proved application against immunomodulation, anti-pyretic, analgesic, cytoprotective and anti-tussive (Nisha *et al*., 2004). Further, it is useful in memory enhancing, and ophthalmic disorders. It is also helpful in neutralizing snake venom (Singh *et al*., 2011).

### 2.3.1.4 PHYTOCONSTITUENTS OF EMBLICA OFFICINALIS

*Emblica officinalis* are rich in tannins, alkaloids, phenolic compounds, vitamin C, acid, ellagic acid, phyllembelin, protein, carbohydrates, glucose, fibres, phosphorus, iron and calcium. Compounds isolated from EO have a wide range of phytochemical
components including terpenoids, alkaloids, flavonoids, and tannins. The fruits, leaves and bark are rich in tannins. Likewise the root contains ellagic acid and lupeol and bark contains leucodelphinidin. The immature fruit was found to contain indole acetic acid and auxins al, a3, a4 and a5. In addition, the seeds yield a fixed oil (16%), and it consists of fatty acids namely linolenic (8.8%), linoleic (44.0%), oleic (28.4%), stearic (2.15%), palmitic (3.0%) and myristic (1.0%). Besides, the phytochemicals of this plant include hydrolysable tannins (punigluconin, Emblicanin A, pedunculagin Emblicanin B,) alkaloids (Phyllantidine and phyllantine), flavonoids (Kaempferol 3-O-alpha L (6” methyl) rhamnopyranoside, Kaempferol 3-O-alpha L (6” ethyl) amnopyranoside) (Ghosal et al., 1996; Khan, 2009).

Furthermore, a new acylatedapigeninglucoside naming apigenin 7-O-(6” butyrylbeta glucopyranoside functional group was isolated from leaves of Phyllanthus emblica together with other known compounds like gallic acid and methyl gallate. Amla is well known for its nutritional qualities (Bhattacharya et al., 2000). It is regarded as one of the richest sources of vitamin C (200-900 mg per 100 g of edible portion). And other components of nutritional importance are moisture 81.2 %, calcium 0.05%, phosphorous 0.02%, iron 1.2 mg/100g and protein 0.5% (Jeena and Kuttan, 1995).

2.3.1.5 TERMINALIA BELLERICA

Terminalia bellerica Roxb. (Combretaceae) is commonly known as “belleric myrobalan” in English, Bibhitaka in Hindi, bahera in Bengali, tushan in Malayalam and akkam and thani in Tamil. It is a large deciduous tree with buttress and bluish or ashy-grey bark, whose fruits are hard, 2-3 cm long, brownish, the surface is velvet and densely covered with hairs. Traditionally, its fruit is used as laxative and purgative in the treatment of fever, diarrhea, piles and dropsy. It is a widely used folk medicine to treat asthma, cancer, headache, hypertension, inflammation and pain. It is consumed as an anti-diabetic drug and for myocardial necrosis by tribals of Assam and Tirap district of Arunachal Pradesh (Anand et al., 1997).
2.3.1.6 PHYTOCONSTITUENTS OF *TERMINALIA BELLERICA*

*Terminalia Bellerica* plant is reported to possess gallic acid, ellagic acid, chebulagic acid, β-sitosterol, tannin, bellericanin, termilignan, thannilignan, arjungenin, anolignan β, flavanolignan, bellericanin, bellericoside, ethyl gallate, galloyl glucose, chebulagic acid, and phyllemblin (Patil *et al.*, 2011).

Figure 2.1: Constituents of triphala
2.3.2 PHARMACOLOGICAL PROPERTIES OF TRIPHALA

2.3.2.1 ANTIMICROBIAL ACTIVITY OF TRIPHALA

Inhibitory activity of triphala was reported against common bacterial isolates including *Pseudomonas aeruginosa, Klebsiella pneumoniae, Shigella sonnei, Shigella flexneri, Staphylococcus aureus, Vibrio cholera, Salmonella paratyphi-B, Escherichia coli* and *Salmonella typhi* (Srikumar *et al.*, 2007). A recent study demonstrated the inhibitory effects of triphala against multidrug-resistant uropathogenic bacteria (Bag *et al.*, 2013). These studies support the anti-bacterial activity of triphala against bacterial isolates.

2.3.2.2 IMMUNOMODULATORY ACTIVITY OF TRIPHALA

Immunomodulatory effect of triphala is found to be defensive against emerging contagious infections (Srikumar *et al.*, 2005). Several researchers emphasized the synergistic effect of triphala in restoring and invigorating the immune system (Belapurkar *et al.*, 2014). Triphala has also been proven to enhance the neutrophil functions in stress induced alteration in immunized rats. Triphala is also found to possess significant immunostimulatory effect on cellular immune response, especially cytotoxic T cells and natural killer cells (Phetkate *et al.*, 2012).

2.3.2.3 RADIOPROTECTIVE EFFECT OF TRIPHALA

Studies have shown that intraperitoneal injection of triphala protected mice from radiation induced mortality. It is worth mentioning that triphala modulated the activities of the significant enzymes, superoxide dismutase and xanthine oxidase (XO) prone to be affected by radiation exposure (Jagetia *et al.*, 2002).

2.3.2.4 ANTI-TUMOR EFFECT OF TRIPHALA

Triphala is emerging as a potential anticancer drug in the recent years. Several researchers have stressed the importance of triphala as a potential anti-carcinogenic agent. Since triphala has tumor specific cytotoxic effects, without impairing normal cells. A recent study showed that triphala could induce angiogenesis by suppressing vascular
endothelial growth factor receptor-2 phosphorylation, hence revealing its anti-tumor activity (Deep et al., 2005; Lee et al., 2015). It is also found to be effective in killing cancer cells in-vitro and inhibit transplanted mouse tumors in-vivo (Sandhya et al., 2006). In addition, it has also been effective in inducing apoptosis in human pancreatic cell line Capan-2 in-vitro (Shi et al., 2008). An experimental study by Kaur et al. (2005) showed that acetone extract of triphala exhibits significant cytotoxic effect on Shionogi 115 (S115), MCF-7 breast cancer cells, PC-3 and DU-145 prostate cancer cell lines.

2.3.2.5 ANTIOXIDANT EFFECT OF TRIPHALA

Evidence from in-vitro studies suggested that aqueous extract of triphala has shown greater efficiency against lipid peroxidation and significant radical scavenging activity (Sabu and Kuttan, 2002; Naik et al., 2005). Triphala was also effective in preventing superoxide-induced haemolysis of red blood cells (Vani et al., 1997). Recent findings by Babu et al. (2014) suggest that triphala could contribute significantly to slowing down the process of aging and other stress-related degenerative disorders.

2.3.2.6 ANTI-CARIES ACTIVITY OF TRIPHALA

Dental caries is one of the most commonly occurring infections globally, irrespective of age, sex, and race. Current anti-plaque therapies available in the market have shown several undesirable side-effects that necessitates the urge to search for alternative plant-based agents (Emilson, 1994) Studies have shown that triphala is beneficial in preventing several oral diseases such as gingivitis, bleeding gums and dental caries (Jagtap and Karkera, 1999). Terminalia chebula, one of the constituents of triphala extract successfully inhibited the plaque formation on the surface of the tooth by preventing the sucrose-induced adherence and the glucan induced aggregation. Thus, the extract could act as a useful agent in treating carious teeth, by virtue of its microbicidal property and protecting the teeth from further demineralization and the breakdown of the tooth enamel (Prakash and Shelke, 2014).
2.3.2.7 ANTI-COLLAGENASE ACTIVITY OF TRIPHALA

A recent report stated that triphala reduced the matrix metalloproteinase-9 (MMP-9) and polymorphonuclear leukocytes (PMNLs) activity expressed in adult periodontitis patients more effectively than positive control doxycycline. Doxycycline is the most potent tetracycline for collagenase/gelatinase inhibition. However, its long term use has certain known disadvantages. The use of triphala at 1500 μg/ml concentration has shown a protective effect against PMN-type collagenase, especially MMP-9 degradation. In addition, clinical studies with human volunteers have also shown that triphala (6%) was as effective as chlorhexidine (0.1%) in preventing dental caries. Besides this, triphala is also proved to inhibit microbial counts of Lactobacillus, and Streptococcus mutans, a biofilm-producing dental pathogen (Desai and Debnath, 2010).

Besides these stupendous medicinal properties of triphala, there remains very sparse information on potential mechanisms underlying the anti-inflammatory action of triphala on inflammatory cascades and/or cellular signaling pathways, which merits further studies to fully elucidate the anti-arthritis botanicals and their mechanisms of action.