Natural products as a gold mine for arthritis treatment

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Arthritis, an inflammation of the joints, is usually a chronic disease that results from dysregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor and interleukin-1β) and pro-inflammatory enzymes that mediate the production of prostaglandins (e.g. cyclooxygenase-2) and leukotrienes (e.g. lipooxygenase), together with the expression of adhesion molecules and matrix metalloproteinases, and hyperproliferation of synovial fibroblasts. All of these factors are regulated by the activation of the transcription factor nuclear factor-κB. Thus, agents that suppress the expression of tumour necrosis factor-α, interleukin-1β, cyclooxygenase-2, lipooxygenase, matrix metalloproteinases or adhesion molecules, or suppress the activation of NF-κB, all have potential for the treatment of arthritis. Numerous agents derived from plants can suppress these cell signaling intermediates, including curcumin (from turmeric), resveratrol (red grapes, cranberries and peanuts), tea polyphenols, genistein (soy), quercetin (onions), silymarin (artichoke), guggulsterone (guggul), boswellic acid (salai guggul) and withanolides (ashwagandha). Indeed, several preclinical and clinical studies suggest that these agents have potential for arthritis treatment. Although gold compounds are no longer employed for the treatment of arthritis, the large number of inexpensive natural products that can modulate inflammatory responses, but lack side effects, constitute 'goldmines' for the treatment of arthritis.

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Current Opinion in Pharmacology 2007, **7**:344–351

This review comes from a themed issue on
Musculoskeletal pharmacology
Edited by Alan Harvey and Edward Rowan

Available online 1st May 2007

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2007.03.002

Introduction

Although there are more than 100 different kinds of arthritides, the three most common in the Western world are gout, osteoarthritis (OA) and rheumatoid arthritis (RA).

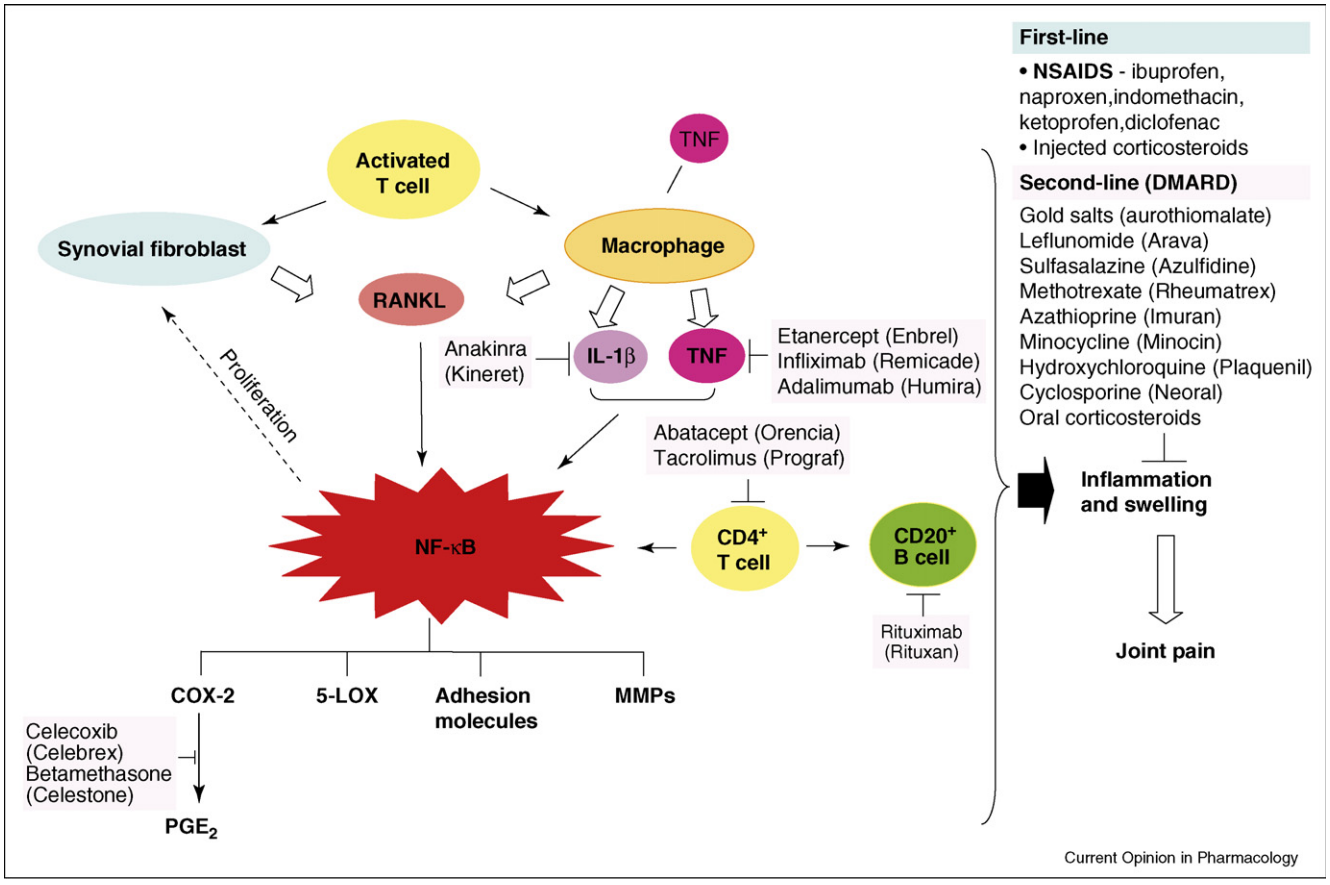
Gout occurs in response to the presence of monosodium urate (MSU) crystals in joints, bones and soft tissues, and is usually treated by non-steroidal anti-inflammatory drugs (NSAIDs), oral or intravenous colchicines, and oral, intravenous or intrarticular glucocorticoids. All can abort acute attacks, but they also may have severe side effects.

OA results from articular cartilage failure induced by a combination of genetic, metabolic, biochemical and biomechanical factors. OA is normally treated with analgesics such as acetaminophen and opioids, NSAIDs, and intra-articular therapies such as glucocorticoids and hyaluronans.

In RA, 75% of the sufferers are women, suggesting the importance of hormones in the etiologoy of the disease. Smoking and stress are also thought to contribute to this disease, which is characterized by joint stiffness and swelling, often in a symmetrical pattern on both sides of the body. The goals of management of patients with RA are to control pain and swelling, delay disease progression, minimize disability, and improve quality of life. For pain control and swelling, treatment includes analgesics such as acetaminophen and opioids, NSAIDs, and intra-articular therapies such as glucocorticoids. In addition, disease-modifying anti-rheumatic drugs (DMARDs) are used to modify the clinical and radiological course of RA. Examples include methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine and newer therapies such as anti-tumour necrosis factor (TNF)-α therapy (etanercept, infliximab and adalimumab), anti-CD20 therapy (rituximab) and abatacept (Figure 1). However, all of these agents are associated with numerous side effects.

Arthritis, a disease of the joints, is primarily a pro-inflammatory disease. As such, a better understanding of the pro-inflammatory nature of arthritis is essential if new therapies are to succeed. The cell signalling network that mediates the inflammatory response during arthritis is depicted in Figure 1. The role of inflammatory cytokines such as TNF-α, interleukin (IL)-1β, IL-6 and chemokines; inflammatory enzymes such as cyclooxygenase (COX)-2, 5-lipoxygenase (5-LOX) and matrix metalloproteinase

Figure 1



Pathophysiology of inflammatory arthritis. The figure shows current therapeutic targets and their sites of action.

(MMP)-9; and adhesion molecules in the pathogenesis of arthritis is well documented [1–3]. Almost all of the inflammatory mediators linked to arthritis have been shown to be regulated by the transcription factor nuclear factor-κB (NF-κB) [4]. Like most other autoimmune diseases, arthritis is more prevalent in the Western world than in other countries [5•]. Although the reason for this is not fully understood, lifestyle is known to play a major role, and dietary constituents could explain the geographical variation in incidence. Because current treatments for arthritis result in unwanted side effects and tend to be expensive, natural products devoid of such disadvantages offer a novel opportunity. Thus, the current review is a detailed discussion of the potential of natural agents for treatment of arthritis (see Table 1).

Potential of natural agents against arthritis

Agents derived from plants that can modulate the expression of pro-inflammatory signals clearly have potential against arthritis (Table 1). These include flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins and anthoxanthins, all of which are known to have anti-inflammatory effects. Some of these polyphenols, which have been tested for the treatment of arthritis, are discussed below. The chemical structures of these agents are shown in Figure 2.

Curcumin (*Curcuma longa*)

Curcumin (diferuloylmethane) is a yellow colouring agent present in turmeric (*Curcuma longa*) that has been used for centuries as a spice on the Indian subcontinent [6]. Curcumin has been well documented in Ayurveda, an Indian system of medicine, as an anti-inflammatory agent. Several lines of evidence, both *in vitro* and *in vivo*, suggest that curcumin may have potential against arthritis. The work from our laboratory and others have shown that curcumin can downregulate activation of the transcription factor NF-κB [7], thus leading to downregulation of the expression of TNF-α [8•], adhesion molecules [9], MMPs [10••], COX-2 [10••], 5 –LOX [11] and other inflammatory intermediates [12], all of which are associated with arthritis.

That curcumin indeed has potential against arthritis was first reported in 1980 [13]. Neutral matrix MMPs are responsible for the pathological features of RA such as

Table 1

Molecular targets of natural products that exhibit anti-arthritic potential.

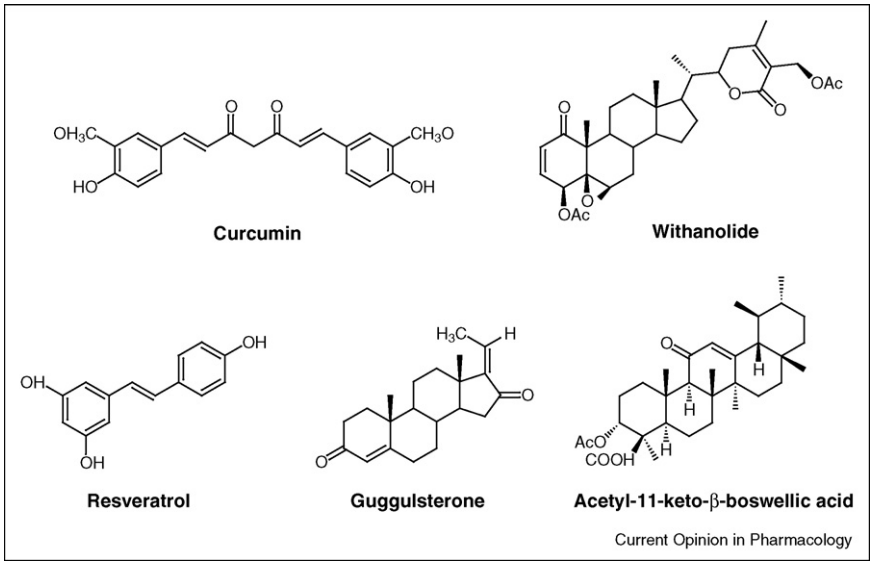
Compounds	Source	Molecular targets	References
Boswellic acid	*Boswellia serrata (Salai guggul)*	NF-κB, COX-2, 5-LOX, MMP-9, ICAM-1	[37,38•]
Berberine	*Berberis vulgaris* (barberry)	NF-κB, COX-2, TNF-α, IL-1β, IL-6	[52]
Celastrol	*Tripterygium wilfordii*	NF-κB, COX-2, MMP-9, TNFα, AMs	[53,54••]
Cucurbitacin R	*Cayaponia tayuya*	NF-κB, COX-2, TNF-α	[55]
Curcumin	*Curcuma longa* (tumeric)	NF-κB, COX-2, 5-LOX, TNF-α, IL-1β, IL-6, IL-8, MMPs, AMs	[6]
Eugenol	*Syzygium aromaticum* (cloves)	NF-κB, COX-2, 5-LOX, TNF-α, IL-1β	[56]
Guggulsterone	*Commiphora mukul* (guggul)	NF-κB, COX-2, MMP-9	[27,31]
Genistein	*Glycine max* (soybeans)	NF-κB, TNF-α, IL-1β, IL-6	[57]
Luteolin	*Thymus vulgaris* (thyme)	NF-κB, COX-2, TNFα	[58]
Morin	*Chlorophora tinctoria (*fustic*)*	NF-κB, COX-2, 5-LOX, MMP-9, TNF-α, IL-1β, IL-6	[59]
Quercetin	*Allium cepa* (onions)	NF-κB, COX-2, TNF-α, 5-LOX, TNF-α, IL-1β, AMs	[60]
Resveratrol	*Vitis vinifera* (red grapes)	NF-κB, COX-2, TNF-α, 5-LOX, AMs	[23,25]
Rosmarinic acid	*Rosmarinus officinalis (*rosemary*)*	NF-κB, COX-2, TNF-α, AMs	[61,62]
Silymarin	*Silybum marianum* (milk thistle)	NF-κB, COX-2, TNF-α, 5-LOX, AMs	[63]
Statins	*Aspergillus terreus* (yeast)	NF-κB, COX-2, MMP-9, AMs	[64•,65]
Tea polyphenols	*Camellia sinensis* (black tea)	NF-κB, COX-2, TNF-α, 5-LOX, AMs, MMPs	[66]
Ursolic acid	Ocimum sanctum (holy basil)	NF-κB, COX-2, MMP-9	[67,68]
Withanolides	*Withania somnifera (Ashwagandha)*	NF-κB, COX-2, MMP-9, ICAM-1	[32••,33]

AM, adhesion molecule; ICAM-1, intercellular adhesion molecule-1.

degradation of cartilage; however, the upregulation of MMP mRNA associated with arthritis was inhibited by curcumin [14]. This polyphenol has also been shown to suppress the expression of TNF-α-induced MMP-13 in primary chondrocytes [15]. Jackson *et al*. [16] found that curcumin inhibited neutrophil activation, synoviocyte proliferation, angiogenesis, and collagenase and stromelysin expression, thus suggesting that curcumin has therapeutic potential in arthritis. It has also been reported to potentiate the growth-inhibitory and pro-apoptotic effects of the COX-2 inhibitor celecoxib in osteoarthritis synovial adherent cells [17]. Indeed, a recent study showed that the suppression of NF-κB activation by curcumin leads to inhibition of the expression of COX-2 and MMP-9 in human articular chondrocytes [18].

Besides *in vitro* studies, *in vivo* studies also suggest that curcumin might have potential against arthritis. For example, oral administration of curcumin has been shown to decrease elevated levels of the glycoprotein Gp A72, with concomitant lowering of paw inflammation in arthritic rats [19]. Funk *et al*. [20] determined the *in vivo*

Figure 2



Chemical structure of several compounds (mentioned within in the text) with anti-arthritic potential.

efficacy of curcumin in the prevention or treatment of arthritis using streptococcal cell wall-induced arthritis, a model of RA. In this model, curcumin prevented joint inflammation when treatment was started before, but not after, the onset of joint inflammation.

Resveratrol (*Vitis vinifera*)

Resveratrol (or *trans*-3,5,4′-trihydroxystibene) was first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum O. Loes*), but has since been found in various plants including grapes, berries and peanuts [21]. The work from our laboratory has shown that resveratrol can suppress the activation of NF-κB [22] and downregulate inflammatory gene products such as COX-2, 5-LOX, IL-1β, and IL-6 [23], all of which play a crucial role in arthritis. Recent studies indicate that this stilbene might play a role in the prevention and treatment of arthritis; for example, Tang *et al.* showed that resveratrol can suppress the proliferation, and induce caspase-3-mediated apoptosis, of synoviocytes *in vitro* [24].

Elmali and colleagues determined the *in vivo* effects of intra-articular injections of resveratrol on cartilage and synovium in an experimental OA model in rabbits [25,26]. They found that resveratrol significantly reduced cartilage tissue destruction, and hence concluded that resveratrol could protect cartilage against the development of experimentally induced OA. Well-designed clinical trials are now needed to establish the efficacy of resveratrol in the prevention and treatment of arthritis.

Guggulsterone (*Commiphora mukul*)

Guggulsterone [4,17(20)-pregnadiene-3,16-dione] is a plant sterol derived from the gum resin (*guggulu*) of the tree *Commiphora mukul*. This sterol can inhibit NF-κB activation and downregulate the expression of inflammatory gene products such as COX-2 and MMP-9, which are major players in the development of arthritis [27]. We also showed recently that guggulsterone can suppress osteoclastogenesis induced by RANKL (receptor activator of NF-κB ligand), a bone-resorbing cytokine [28•].

The anti-arthritic and anti-inflammatory activities of gum guggul were first demonstrated by Gujral *et al.* in 1960 [29]. Subsequently, the anti-inflammatory activity of *C. mukul* (guggul) has been compared with that of NSAIDs, namely phenylbutazone and ibuprofen [30]. In this study, an inflammatory syndrome resembling RA in humans was induced in the right hock joint of albino rabbits by intra-articular injection of mycobacterial adjuvant in liquid paraffin. Development of this arthritic syndrome was studied for a period of five months, with and without drug treamtment. Anti-inflammatory agents such as phenylbutazone, ibuprofen and fraction 'A' of gum-guggul from *C. mukul* were administered orally at a daily dose of 100 mg/kg, 100 mg/kg and 500 mg/kg, respectively, for a period of five months. All three drugs decreased joint swelling. These results highlight the beneficial role of phenylbutazone, ibuprofen and fraction 'A' of gum-guggul in experimental arthritis. In another study, Singh *et al.* [31] conducted both preclinical and clinical investigations of guggul for the reduction of pain, stiffness, improved function and tolerability in older patients with a diagnosis of OA of the knee. They demonstrated significant improvement in patients during the trial, in both Western Ontario and McMaster Universities (WOMAC) and visual analogue 'scales' and objective measures used for assessment purposes. There were no side effects reported during the trial. Therefore, guggul appears to be a relatively safe and effective supplement to reduce symptoms of OA.

Withanolide (*Withania sominifera*)

Withanolides, which are extracted from *Withania somnifera*, are employed in the treatment of arthritis and are known to be potent inhibitors of angiogenesis, inflammation and oxidative stress. Our group showed for the first time that withanolides can indeed inhibit the activation of NF-κB and NF-κB-regulated gene expression [32••], which could explain their anti-arthritic actions.

Begum and Sadique [33] showed for the first time the long-term effects of *W. somnifera* on adjuvant-induced arthritis in rats. More recently, Rasool and Varalakshmi [34] investigated the effect of *W. somnifera* root powder on paw volume and serum lysosomal enzyme activities in rats in which arthritis was induced with MSU crystal. In addition, the levels of β-glucuronidase and lactate dehydrogenase were measured in MSU crystal-incubated polymorphonuclear leucocytes. Significant increases in both paw volume and the levels of serum lysosomal enzymes were observed in rats with MSU crystal-induced arthritis. Increased β-glucuronidase and lactate dehydrogenase levels were observed in untreated polymorphonuclear leucocytes incubated with MSU. Upon treatment with *W. somnifera* root powder (500 mg/kg to 1000 mg/kg), β-glucuronidase and lactate dehydrogenase levels reverted to near normal. *W. somnifera* also displayed potent analgesic and antipyretic effects, without any sign of gastric damage, at different doses in experimental rats; the NSAID indomethacin was used as a standard. These results provide evidence for the suppressive effect of *W. somnifera* root powder on arthritis by reducing amplification and propagation of the inflammatory response, without causing any gastric damage.

Boswellic acid (*Boswellia serrata*)

Boswellic acid (BA) is an active component of *Boswellia serrata* (also known as Salai guggul). Extensive research in the past 30 years identified the active component of this resin as BA (a pentacyclic triterpenic acid) and its derivatives (acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid). In animal models of inflammation, BA has been shown to be an effective

adjuvant mitigating bovine serum albumin-induced arthritis [35,36] and OA [37]. The anti-arthritic potential of BA is a result of its anti-inflammatory activity, mediated through inhibition of NF-κB, COX-2 and 5-LOX [38•,39].

Kimmatkar *et al.* [37] conducted a randomized double-blind placebo-controlled crossover study to assess the efficacy, safety and tolerability of *B. serrata* extract in 30 patients with OA of the knee. During the study, 15 patients each received active drug or placebo for eight weeks. After the first intervention, washout was given and the groups were 'crossed over' to receive the opposite intervention for eight weeks. All patients receiving drug treatment reported a decrease in knee pain, increased knee flexion, and increased walking distance. Furthermore, the frequency of swelling in the knee joint was decreased. The observed differences between drug- and placebo-treated patients were statistically significant and clinically relevant. *B. serrata* extract was well tolerated, except for minor gastrointestinal adverse drug reactions. Fan *et al.* [40] examined the effects of an acetone extract of *Boswellia carterii* gum resin on adjuvant-induced arthritis in Lewis rats. The results show that *B. carterii* extract had significant anti-arthritic and anti-inflammatory properties, and suggest that these effects may be mediated via the suppression of pro-inflammatory cytokines. Further studies are needed to fully realize the potential of this agent in the treatment of arthritis.

Others

Several other natural compounds have also been found to exhibit anti-arthritic potential. For example, 6-shogaol — a component of the ginger rhizome — could have anti-inflammatory properties. Levy *et al.* [41] found that 6-shogaol reduced the chronic inflammatory response in the knees of rats treated with complete Freund's adjuvant. This effect of 6-shogaol was associated with significantly lower concentrations of soluble vascular cell adhesion molecule-1 in the blood, and reduced infiltration of leukocytes (including lymphocytes and monocytes/macrophages) into the synovial cavity of the knee.

Clinical trials

Clinical trials have been conducted with several natural products, as well as formulations containing combinations of the above-mentioned agents.

Avemar, a wheat germ extract, was used as adjunct therapy in patients with RA who had failed on at least two DMARDs in an open-label trial. The joint score, as well as functional status, improved after one year. In addition, patients could reduce the dose of glucocorticoids needed to control symptoms, suggesting that avemar has good efficacy [42].

Similarly, Meta050 (a mixture of reduced iso-alpha acids, rosemary plant extract and oleanolic acid) produced significant pain relief in patients with RA in an eight-week open trial [43]. Fish oil containing omega 3 fatty acids has been shown to reduce inflammation and, in RA, its use reduces joint disease activity. A recent study shows it is more effective when used with olive oil [44]. In a 20-week placebo-controlled study of ethanolic extract of *Tripterygium wilfordi* hook F (TWHF), a dose-dependent effect was seen in the American College of Rheumatology 20 (ACR20) response in patients with RA. Diarrhea was the major side effect seen with TWHF [45]. Ginger has also been used traditionally in various Ayurvedic medicines. Concentrated extract from ginger improved pain and the WOMAC index, as well as the requirement for analgesics, in patients with OA. It was associated with a modest benefit, with minimal toxicity related to the gastrointestinal tract [46]. Avocado/soyabean unsaponifiables are more effective than placebo in relieving pain in patients with OA when used in a dose of 300–600 mg/d [47]. Willow bark extract has also been tested in a double-blind placebo-controlled study and provided significant pain relief in patients with OA [48].

Formulations containing a mixture of natural products also reduce inflammation and disability in patients with RA. Kulkarni *et al.* [49] examined the clinical efficacy of a herbomineral formulation containing roots of *W. somnifera*, the stem of *B. serrata*, rhizomes of *C. longa* and a zinc complex (articulin-F) in a randomized, double-blind, placebo-controlled, crossover study in patients with OA. After a one-month single blind run-in period, 42 patients with OA were randomly allocated to receive either a drug treatment or a matching placebo for a period of three months. After a 15-day wash-out period, the patients were transferred to the other treatment for another three months. Clinical efficacy was evaluated every fortnight on the basis of severity of pain, morning stiffness, Ritchie articular index, joint score, disability score and grip strength. Treatment with the herbomineral formulation significantly reduced pain and the disability score.

RA-11, a polyherbal preparation used by Ayurvedic physicians that contains extracts of *W. somnifera*, *B. serrata*, *Zingiberis officinale* and *C. longa*, was tested in a double-blind placebo-controlled study and was found to reduce joint swelling and rheumatoid factor levels. However, no significant difference was seen in the ACR 50 response between the two groups. This trial is one of the best regarding the power of study, as well as having well-defined outcome variables [50]. Chopra *et al.* [51] also evaluated the efficacy and safety of RA-11 in patients with symptomatic OA of the knees in a randomized, double-blind, placebo-controlled trial at a single-centre 32-week drug trial. This controlled drug trial demonstrated the potential efficacy and safety of RA-11 in the symptomatic treatment of OA knees over 32 weeks of therapy.

Even though there have been a large number of clinical trials of natural products, most were underpowered, meaning that they could not detect clinical benefit or did not compare standard care with natural drugs. Furthermore, most trials have shown only a modest clinical benefit, with the comparison group usually being a placebo rather than a known effective agent. There is a need to develop well-designed clinical trials to assess the true potential of herbal medicines in arthritis, and especially in OA and RA. In RA, the natural product should be compared with MTX in MTX-naive patients or in patients with partial response to MTX as an additional therapy. Alternatively, natural products could be studied in patients with significantly toxic reactions to conventional drugs, as natural products have a good safety profile. The essential ingredients in most natural products are not precisely defined. Identification of the active moiety in such products could help in the design of better molecules for treatment.

Conclusions

Although numerous treatments for various forms of arthritis have been identified, they suffer from various drawbacks, such as lack of efficacy, excessive side effects and high cost. Usually, treatment of arthritis requires treatment of the patient for their entire lifetime, and so these drawbacks are significant. Plant-derived products offer much promise but they require extensive investigation in various preclinical and clinical settings to prove their usefulness. Owing to the lack of intellectual property rights, the industry currently has little motivation to pursue such studies. Hopefully, federal agencies will provide the financial backing to support such studies. Thus, natural products serve as a gold mine for the treatment of arthritis.

Acknowledgements

This research was supported by The Clayton Foundation for Research (to BBA), and by P50 Head and Neck SPORE grant from National Institute of Health (to BBA). Dr Khanna is supported by the Scleroderma Foundation (New Investigator Award) and a National Institutes of Health BIRCWH Award (grant#HD051953). We would like to thank Walter Pagel for a careful review of the manuscript.

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