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Review Article

PHYTOCHEMICALS IN THE TREATMENT OF ARTHRITIS: CURRENT KNOWLEDGE

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ABSTRACT

The objective of the present review is to evaluate the therapeutic potential of phytochemicals against arthritis, which is asymptomatic disorder of chronic joint inflammation followed by swelling and pain. Here, we discussed about the anti-arthritic activity of many phytomolecules such as Norisoboldine, Berberine, Triptolide, Hesperidin Hesperidin, Madecassocide, Hydroxy napthoquinone, Ginsenoside, Cryptotanshinone, Kirenol, Thymoquinone, Chlorogenic acid, Curcumin, Bromelain, Andrographolide and Allicin. These compounds are able to control inflammatory responses, proinflammatory cytokines, osteoclast differentiation and to prevent bone erosion in the joints. In this article, we reviewed anti-arthritic activities of phytichemicals from 2011-2019, using various scientific websites like PubMed, Google Scholar, Science Direct etc. Till date clinical trials conducted with anti-arthritic phytomolecules are very less. Hence, more clinical trials are needed to bring plant molecules as safe and effective anti-arthritic drugs in the market, either alone or in combination with other anti-arthritic agents.

Keywords: Phytochemicals, Anti-arthritic agents, Rheumatoid arthritis, Osteoarthritis, Chronic inflammation, Autoimmune disease

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INTRODUCTION

Arthritis is not actually a disease; it is a symptomatic disorder of chronic joint inflammation followed by swelling and pain. It occurs due to malfunctioning of the immune system or, from the family background or, from some injuries of joints in childhood. It can affect the cartilages and bones places around the affected joints and the internal organs like eyes, heart and lungs. Arthritis usually observed in the hand, feet or, wrist of the human body [1].

Arthritis is especially of two types, rheumatoid arthritis (RA) and osteoarthritis (OA). RA is an autoimmune disease followed by chronic inflammation. This type of arthritis is happen due to hyperplasia of synovial membrane, which causes large-scale bone destruction around the joints. Some symptoms are there like pain, stiffness, restricted movement etc. with cardiovascular, skeletal and physiological disorders. There are some medications such as nonsteroidal anti-inflammatory drugs (NSAID's) and steroids, which can control RA [2-4]. But these NSAID's have some side effects such as such as gastric ulceration and acute renal failure [3-7]. Women's are more affected by RA rather than men [8]. In another side OA is a disease of articular cartilage i.e. protective tissue present at the end of the joints, which is wearing down day by day. It is causes joint pain and disability in movement followed by formation of osteophyte, joint space narrowing and chronic synovial inflammation. It also affect entire synovial joint like synovium, meniscus, ligaments etc [9]. Approximately 1.8 million of people suffering with RA in United States of America and the actual causes till unknown and these complications make the disease more expensive. Some scientists are conceiving that the future treatment of RA may be based on the two things, one is imprinting and another one is epigenetics [10]. Rheumatoid arthritis is generally happening in developed countries like US, than developing countries like China. The female to male ratio for this disease is about 2-3:1 [11]. Osteoarthritis is also affecting more women after menopause than in men and it affects mainly the joints of hands, hips and knees. It is actually a disease cause's cartilage degradation in the joints and the most significant cause disability in the world [12].

Phytochemicals are most helpful in the treatment of arthritis, which are very much effective in inflammatory, autoimmune and infectious diseases [13]. In the present review, we have summarized systematically the literature data on the phytochemical and pharmacological investigations for the treatment of arthritis that have been reported from the year 2011 to 2019, using various scientific websites. Chemical structures of various phytochemicals used in the treatment of arthritis are summarized in fig. 1. Our aim is to focus the recent scientific evidence in our review paper, trying to find the right mechanisms of these phytocompounds against arthritis.

Different phytomolecules as anti-arthritic agents

Berberine

Berberine is an isoquinoline alkaloid, shown the therapeutic activity on so many autoimmune diseases including rheumatoid arthritis. It was given through oral route because its anti-arthritic effect was gut dependent. The intestine is responsible for secretion of neuropeptides, hormones and cytokines; which are regulated by the herbal drug berberine. It ameliorates collagen-induced arthritis by the reduction of bone destruction on joint and can be suppressing Th17 cell frequency and interleukin-17 level in blood [14]. The dose of berberine is 200 mg/kg per day, which has a significant effect on swollen paw edema. This help to decrease the level of interleukin-17A and immunoglobulin G and it also prevented bone erosion partially [15]. Berberine is found from *Coptidis rhizome* and was used as an antitumor and anti-inflammatory agent. But nowadays it is showing its effects by treating rheumatoid arthritis fibroblast like synoviocytes (RAFLSs) and can also be reduce the cyclin-dependent

kinase 2, 4 and 6. Berberine shows in an apoptosis assay that it is responsible for the apoptotic death of RAFLSs [16].

Triptolide

Triptolide, chemically diterpene triepoxide is a major extract found from the Chinese herb, *Tripterygium wilfordii* Hook F. It showed an immunosuppressive activity in the treatment of rheumatoid arthritis. It has the ability to impede bone destruction in joints but due to its multiorgan toxicity and poor water solubility, it could not be used easily in clinical practice. Although it has a good promising activity in the treatment of rheumatoid arthritis [17]. Triptolide is responsible for damaging of female reproduction capacity, in exposure of 4 hour with the dose 50 and 100 mg/l led to depletion and inactivation of spermatids. After the 24 or 48 hour of exposing it cause in increasing the number of apoptotic cells and decrease in mitotic germ cells and oocytes. Triptolide is used in various treatments like rheumatism, asthma, autoimmune disease, tumors etc. It is also used in organ transplantation [18]. Triptolide showed some adverse effects like liver toxicity, kidney toxicity and myelosuppresion. For reduction of its side effects a nano-drug carrier system was developed. In this system the drug i.e. Triptolide was loaded by poly-gamma-glutamic acid-grafted l-phenylalanine ethylester copolymer. This nano-drug carrier system was characterized by photon scattering correlation spectroscopy and transmission electron microscopy [19].

Norisoboldine

Norisoboldine is an isoquinoline alkaloid, the main chemical constituent of root of *Lindera aggregata*. Norisoboldine exhibited anti-arthritic activity by attenuating osteoclast differentiation and bone erosion via the activation of aryl hydrocarbon receptor (AhR) which helps in the regulation of differentiation of many cells. It also inhibited nuclear factor κB (NF-κB) [20]. Norisoboldine are given as orally for 10 consecutive days, from day 14 to day 23 of adjuvant induced arthritis inducing rats after immunization. Norisoboldine relieved adjuvant-induced arthritis (AIA) rats from the joint destruction by reducing interleukin 6 (IL-6), prostaglandin E2 (PGE2), and matrix metalloproteinase (MMP-13) expression [21]. In a comparative study of the intestinal absorption of norisoboldine in normal and AIA rats, verapamil increased the permeability coefficient (P_{eff}) of norisoboldine by 88% in normal rats and 84% and 86% on day 5 and day 10 in AIA rats, respectively [22]. Norisoboldine exhibited effects on adjuvant-induced arthritis in rats by its pro-apoptotic mechanism [23].

Hesperidin

Hesperidin, a flavanone glycoside was found from the citrus fruits and is known as vitamin P. It reduced nitric oxide, prostaglandin E2 and cyclooxigenase-2 expression in interleukin-1β-stimulated osteoarthritis chondrocytes. It inhibited the inflammatory responses and activation of nuclear factor κB signaling pathway and finally was used as a potent drug for the patients having osteoarthritis [24]. Hesperidin was found in the ethanolic extract of aerial parts of *Rosmarinus officinalis*. Generally this bioflavonoid is found at a greater extent in many plants belonging Rutaceae and Lamiaceae families. It has a significant effect on gout arthritis, combined with ketorolac [25].

Madecassocide

Madecassoside, a triterpenoid was found from the herb *Centella asiatica*. The amount of madecassoside present as active ingredient in that herb is 3.10±4.58 mg in 1 ml and its effective concentration to exert its anti-arthritic action is 10 and 30 µmol/l. It inhibited fibroblast like synoviocyte invasion and migration and it also suppressed matrix metalloproteinase-13 transcription. It down-regulated the phosphorylation and translocation of NF-κB [26]. Madecassoside has an excellent anti-rheumatoid effect with low bioavailability in oral administration. It can regulate inflammatory cytokine interleukin-10. It cannot be given interperitoneal or any other route except oral because it exerted the anti-arthritic action via intestine-dependent manner, not by absorption into blood [27]. It was considerably decreased the pad swelling of monosodium urate triggered mice and inflammation of joint with gouty arthritis. Gout is a type of arthritis which is caused by deposition of monosodium urate crystals on joints. It ameliorate monosodium urate induced neutrophil cytosolic factor-1 and caspase-1. Madecassoside shows the action on lowering the level of urate and also improved renal dysfunction [28].

Hydroxy napthoquinone

Plumbagin, a 5-hydroxy 2-methyl 1,4-napthoquinone is a secondary metabolite of *Arnebia euchroma* plant. It gave a significant effect on inflammation and arthritis at a dose of 2 and 6 mg/kg, when it was checked into a collagen-induced arthritis rat for 12 to 32 d as a daily manner. The development of arthritis is prevented by inhibition of proinflammatory cytokines and by regulation of the balance between Th17 cells and regulatory T cells [29]. It protected joint destruction by decreasing the level of interleukin-1β and showed anti arthritic activity by suppressing paw swelling of Freund's adjuvant arthritis and collagen-induced arthritis models [30]. Another compound Lapachol containing hydroxy napthoquinone group has also a significant effect on autoimmune arthritis. It markedly suppressed the progression of collagen-induced arthritis and antigen-induced arthritis. It was used as a potential therapeutic agent for rheumatoid arthritis due to its inhibitory action on dihydroorotate dehydrogenase [31].

Ginsenoside

The compound ginsenoside produce a by-product compound K, after the degradation by intestinal bacteria. Chemically the compound K is 20-O-D-glucopyranosyl-20(S)-protopanaxadiol. It showed anti-inflammatory and anti-arthritic activities by suppressing cyclooxigenase-2, inflammatory cytokines such as interleukin-1β, tumor necrosis factor-α, interleukin-2 and interleukin-17 respectively [32]. The compound K regulated some cells like endothelial cells, fibroblast synoviosytes, etc, which are involved in rheumatoid arthritis. It was well tolerated due to its lower side effects and was proven as potential agent for treatment of rheumatic diseases [33].

Cryptotanshinone

Cryptotanshinone was obtained from the root of *Salvia miltiorrhiza* plant. It inhibited the action of pro-inflammatory cytokines and suppressed the production and activity of matrix metalloproteinase 9. It also prevented the osteoclast differentiation and nuclear factor κB signaling. Cryptotanshinone showed its effect on collagen induced arthritis in rats for the treatment of rheumatoid arthritis. [34]. This compound exerted its anti-arthritic activity on adjuvant induced arthritis in rats. Cryptotanshinone given intragastric at a dose 50 and 100 mg/kg, and reduced the secondary inflammatory responses. It also inhibited the production of interleukin-1. Cryptotanshinone used in the treatment of rat paw edema and polyarthritis index [35].

Kirenol

Kirenol is chemically a diterpenoid, extracted from the *Herba Siegesbeckiae*, the Chinese herb. Kirenol was able to suppress the inflammatory pathology in collagen-induced arthritis model in rats as well as to suppress the production of interleukin 1β and tumor necrosis factor α in adjuvant arthritis model in rats. It also inhibited synovial hyperplasia, bone erosion and inflammation in the joint of bones [36]. Kirenol clinically and histologically reduced the bovine type II collagen induced arthritis at a dose 2 mg/kg. It ameliorated the levels of tumor necrosis factor α, interleukin-17α and interleukin-6 in synovial fluid, It also upregulated the regulatory T cells [37]. In an *in vitro* experiment, kirenol at a dose of 0-80 µg/ml reduced the pro-inflammatory cytokines. Kirenol was used in the treatment of rheumatoid arthritis as a potential immunosuppressant [38].

Thymoquinone

Thymoquinone, an active constituent of the plant *Nigella sativa* has been used to cure many diseases. It reduced paw weight and improved histological changes in rat model of rheumatoid arthritis. In comparison with methotrexate in pristine induced arthritis, Thymoquinone significantly reduced the clinical score; interleukin-1β and tumor necrosis factor α. Thymoquinone had disease modifying and anti-inflammatory effects [39]. It is called as Kalonji in Southern Asia, its Arabic name is Habat-ul-sauda and black cumin

is its English name. It prevented renal dysfunction, which is associated with rheumatoid arthritis but the efficacy is limited. Thymoquinone and methotrexate both reduced clinical score inflammation, serum creatinine, total leukocyte count, triglyceride, total cholesterol and blood urea. But, Thymoquinone showed similar effectiveness as methotrexate with lesser adverse effects [40]. It showed anti-arthritic effect in Freund's Complete Adjuvant induced arthritic rats by decreasing paw swelling at a dose 10 mg/kg/day. It also showed its anti-inflammatory effects by inhibition of leukotrienes and prostaglandins. Thymoquinone normalized hematological parameters such as lymphocytes, neutrophil, monocytes and hemoglobin concentration. It suppressed the mRNA expression levels of toll-like receptors 2, 4, interleukin-1, nuclear factor κB and tumor necrosis factor α. Thymoquinone may be used as alternative disease-modifying anti-rheumatic drugs in treatment of rheumatoid arthritis. After the administration of Thymoquinone, according to the levels of alanine transaminase, creatinine, aspartate amino-transferase and urea in the serum, stated that it has no nephrotoxic or hepatotoxic effect [41].

Chlorogenic acid

Chlorogenic acid, a phenolic compound, inhibited inflammatory pathway via regulating the gene expression in arthritis. At a dose 30 or 60 mg/kg, Chlorogenic acid decreased joint swelling via inhibiting proinflammatory cytokine production and decreasing the histological damage in bone joint of collagen induced arthritic mice. It also decreased the elevated levels of B cells activating factors (BAFF) at both mRNA and protein levels through the transcriptional activity of BAFF promoter. Chlorogenic acid inhibited the proliferation of fibroblast-like synoviocytes [42]. Chlorogenic acid showed effects on the expression of matrix metalloproteinase-1, matrix metalloproteinase-3, matrix metalloproteinase-13 while increasing the expression of tissue inhibitors of metalloproteinase-1 by investigating through quantitative real-time Polymerase Chain Reaction (PCR) and Enzyme-Linked Immunosorbent Assay (ELISA) at the levels of both protein and mRNA. It suppressed the degradation of inhibitor of κB-α and interleukin-1β induced nuclear factor κB activation. This investigation proved that the Chlorogenic acid may be used as a potent agent for the treatment of osteoarthritis [43]. At a dose of 40 mg/kg, it controlled CD3, CD4 and CD8 of T cell count. Chlorogenic acid suppressed CD80/86 and the helper T cells cytokines. [44].

Curcumin

A yellow hydrophobic polyphenol compound that derived from the herb *Curcuma longa* is named as Curcumin. It was used in many chronic diseases where it acts by metastasis, inhibition of cell proliferation, interleukin-1β, nuclear factor κB and tumor necrosis factor α. Intravenous injection of Curcumin was administered in adjuvant-induced arthritis to study the effect on paw swelling and inflammatory cytokines. Due to its low oral bioavailability it was administered by formulating the drug into oil-water nanoemulsions with a diameter of approx. 150 nm. It showed effect on rheumatoid arthritis by downregulating inflammatory mediators [45]. Curcumin markedly reduced rheumatoid arthritis in 28 d and 48 d at a dose 110 mg/ml/kg/day. Curcumin has complex chemical structure which is responsible for its high pleiotropic activity that has the ability to control many signaling pathways. It reduced the inflammation of joints by suppressing soft tissue swelling, ankylosis and erythema of joints, when was administered as oral supplementation [46]. An experiment was done to check that how to increase the effect of Curcumin. Firstly, Curcumin was mixed with milk and ghee. Then, it was administered to rats through oral route for continuously 21 d. Curcumin showed a significant effect on reducing inflammation of arthritic joints [47].

Bromelain

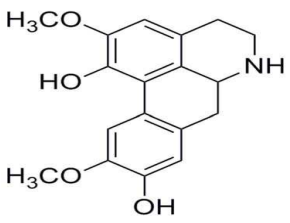
Bromelain is the active ingredient of crude extract of *Ananus comosus*, pineapple, belonging to the family Bromeliaceae. Bromelain was used in the treatment of osteoarthritis in combination with trypsin and rutin. It showed effectiveness in the treatment of osteoarthritis and rheumatoid arthritis in combination with Diclofenac [48]. Bromelain decreased swelling and pain by inhibition of cyclooxigenase-2 (COX-2) and prostaglandin E2 (PGE2) expression in rheumatoid arthritis. It ameliorated the inflammation by protection of cartilage from damage in rheumatoid arthritis at a dose 100 and 500 mg/kg [49]. In an experiment, it showed a significant effect on knee treatment suffering in osteoarthritis at a dose 10 mg/kg [50].

Andrographolide

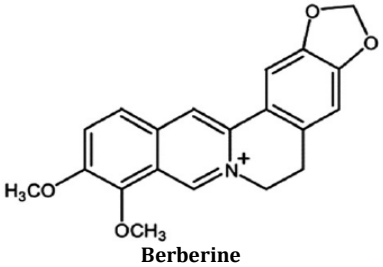
Andrographolide is a diterpenoid lactone isolated from *Andrographis paniculata* and showed anti-inflammatory activity by inhibiting the expression of interleukins and reduced dendritic cells maturation. It also inhibited the translocation of p65 subunit of nuclear factor κB and interfered in binding to the DNA. It was potentially used in treatment of rheumatoid arthritis and other autoimmune diseases by reducing the growth and proapoptotic effects [51]. Methotrexate is widely used for the treatment of arthritis, but due to its hepatotoxicity, it has poor compliance to the patient. Incorporation of Andrographolide with methotrexate increased the strength of methotrexate and exerted hepatoprotective action. The combination of these drugs reduced the levels of serum tumor necrosis factor α, interleukin 1β and interleukin-6. The combined therapy of Andrographolide and methotrexate shows a better treatment against arthritis than a single one by increasing of anti-arthritic activity [52]. Andrographolide was used in rheumatoid arthritis along with joint pain and significantly inhibited Complete Freund's Adjuvant induced rats paw edema by inhibiting the production of nitric oxide and tumor necrosis factor-α in a dose-dependent manner. It suppressed inflammatory responses by inhibiting the signaling pathway and two key inflammatory enzymes. [53]. Andrographolide reduced severity of arthritis and the joint injury by protecting autoimmune arthritis via inhibiting microtubule-associated protein kinase (MAPK) pathways [54].

Allicin

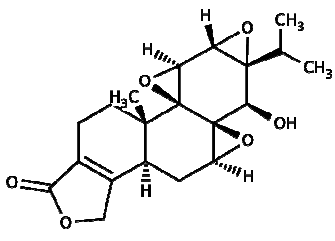
To show the effectiveness of allicin, it was treated in rheumatic conditions, where allicin treatment exhibited the most prominent activity in the treatment of rheumatoid arthritis [55, 56]. In another study, allicin was evaluated for its anti-arthritic activity in albino rats where arthritis was induced by Turpentine and reference drug was used Pioxicam. Finally, allicin exhibited good activity [57]. Lin *et al.* observed the effect of allicin on the IL-1β-Induced inflammatory cytokines in Human Osteoarthritis Chondrocytes [58]. Allicin showed potential in the treatment of ankylosing spondylitis (AS) as an anti-inflammatory agent. Allicin markedly reduces AS perhaps at a dose of 200 mg/kg b.w., via alleviating the secretion of the inflammatory factors in mice [59].



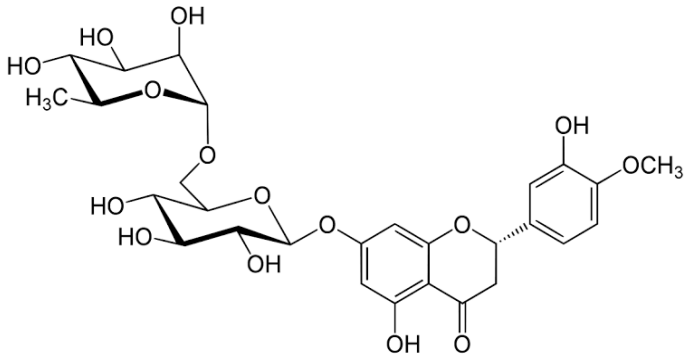
Norisoboldine



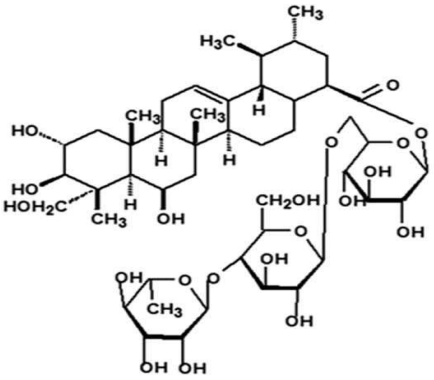
Berberine



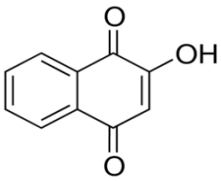
Triptolide



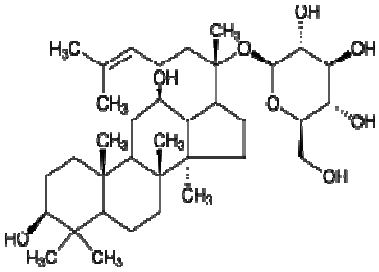
Hesperidin



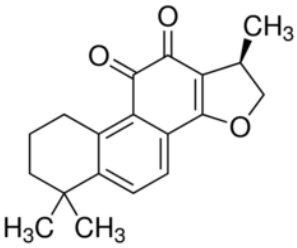
Madecassocide



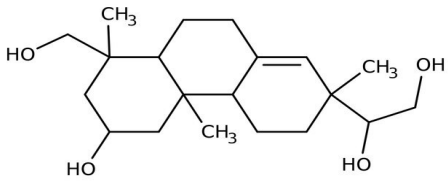
Hydroxy-
-napthoquinone



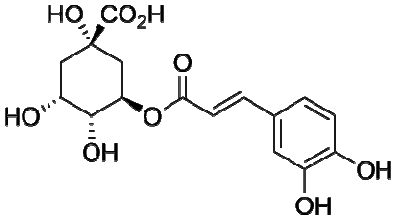
Ginsenoside



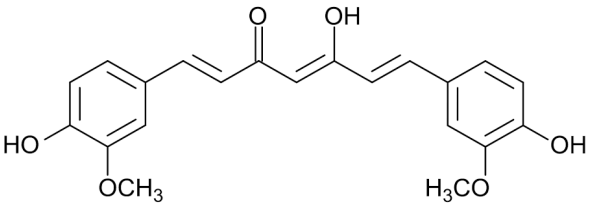
Cryptotanshinone



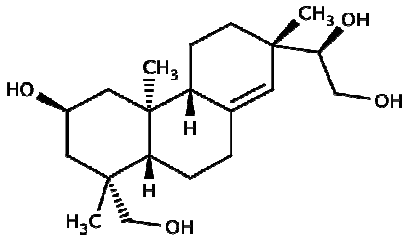
Kirenol



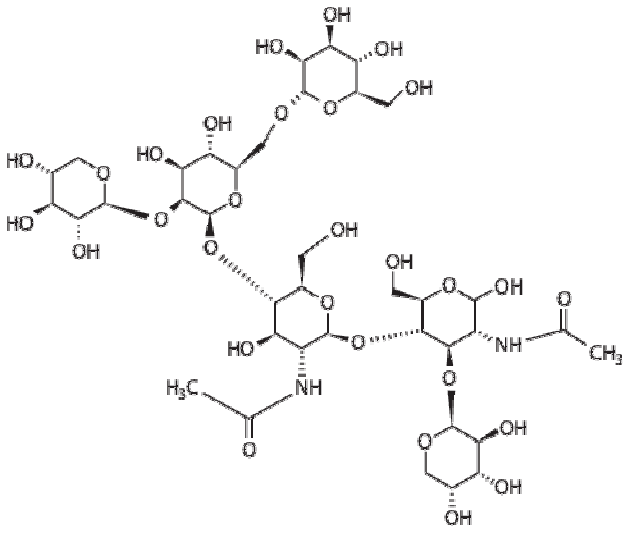
Chlorogenic acid



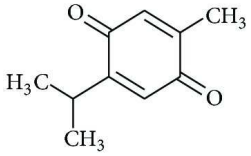
Curcumin



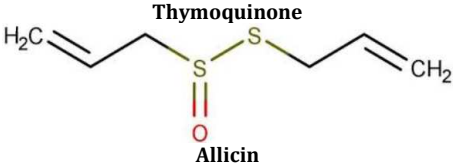
Andrographolide



Bromelain



Thymoquinone



Allicin

Fig. 1: Chemical structures of anti-arthritic phytochemicals

CONCLUSION

Plant is a rich source for the development of novel lead against arthritis. Current knowledge of this review will help the researchers to search for new phytochemicls with anti-arthritic activity. It is very probable that in the coming years, more phytochemicls will get entry into the commercial market as anti-arthritic agents. More clinical trials are needed for this development of safer and effective molecules from plant and to bring them in the market as anti-arthritic drugs, either alone or in combination with other anti-arthritic agents. It is expected that further elucidation of the molecular mechanisms behind the action of these phytochemicals not only can lead to discovery of new drugs for symptomatic relief of arthritic conditions like inflammation and pain, but also can make it possible to stop further progress or even reverse the damage caused by arthritis. From this review it should be evident that there are many bioactive molecules in plants that exert anti-arthritic activity at a particular dose. This review makes an attempt to give current scientific account of use of valuable phytochemicals in arthritis.

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Nil

AUTHORS CONTRIBUTIONS

All of the authors contributed equally.

CONFLICTS OF INTERESTS

Authors have no conflict of interest.

REFERENCES

1. Murugananthan G, Sudheer KG, Sathya CP, Mohan S. Anti-arthritic and anti-inflammatory constituents from medicinal plants. J Appl Pharm Sci 2013;3:161-4.
2. Das N, Bhattacharya A, Mandal SK, Debnath U, Dinda B, Mandal SC, *et al. Ichnocarpus frutescens* (L.) R. Br. root derived phyto-steroids defends inflammation and algesia by pulling down the pro-inflammatory and nociceptive pain mediators: an *in vitro* and *in vivo* appraisal. Steroids 2018;139:18-27.
3. Das S, Mandal SK. Current developments on natural anti-inflammatory medicines. Asian J Pharm Clin Res 2018;11:61-5.
4. Mandal SK. A review on nonsteroidal anti-inflammatory drugs (NSAIDs). Pharmawave 2013;6:12-22.
5. Mandal, SK, Ray SM. Synthesis and biological evaluation of (5,6-dialkoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)acetic acid esters as anti-inflammatory agents with much reduced gastrointestinal ulcerogenic potential. Indo Am J Pharm Res 2014;4:3796-807.
6. Mandal SK, Ray SM. Synthesis and biological evaluation of (6-chloro-3-oxo-2,3-dihydro-1*H*-inden-1-yl)acetic acid esters as anti-inflammatory agents devoid of ulcerogenic potential at the tested dose level. Indo Am J Pharm Res 2014;4:343-50.
7. Mandal SK, Pati K, Bose A, Dey S, De A, Bose S, *et al.* Various ester prodrugs of NSAIDs with low ulcerogenic activity. Int J Pharm Sci Rev Res 2019;54:45-9.
8. Al-Nahain A, Jahan R, Rahmatullah M. Zingiber officinale: a potential plant against rheumatoid arthritis. Arthritis 2014. https://doi.org/10.1155/2014/159089
9. Ravalli S, Szychlinska MA, Leonardi RM, Musumeci G. Recently highlighted nutraceuticals for preventive management of osteoarthritis. World J Orthop 2018;9:255.
10. Khadim MJ, Kaizal AF, Hameed IH. Medicinal plants used for treatment of rheumatoid arthritis: a review. Int J Pharm Clin Res 2016;8:1685-94.
11. Venkatesha SH, Astry B, Nanjundaiah SM, Kim HR, Rajaiah R, Yang Y, *et al.* Control of autoimmune arthritis by herbal extracts and their bioactive components. Asian J Pharm Sci 2016;11:301-7.
12. Castrogiovanni P, Trovato FM, Loreto C, Nsir H, Szychlinska MA, Musumeci G. Nutraceutical supplements in the management and prevention of osteoarthritis. Int J Mol Sci 2016;17:2042.
13. Venkatesha SH, Astry B, Nanjundaiah SM, Kim HR, Rajaiah R, Yang Y, *et al.* Control of autoimmune arthritis by herbal extracts and their bioactive components. Asian J Pharm Sci 2016;11:301-7.
14. Yue M, Xia Y, Shi C, Guan C, Li Y, Liu R, *et al*. Berberine ameliorates collagen-induced arthritis in rats by suppressing Th17 cell responses via inducing cortistatin in the gut. FEBS J 2017;284:2786-801.
15. Yue J, Xu J, Li H, Wang J, Zheng N, Yao H, *et al*. THU0078 berberine ameliorates bone erosions in collagen-induced arthritis rat models via suppressing the expression of il-17a. Ann Rheum Dis 2018;77(Suppl 2):262.2-262.
16. Wang XH, Jiang SM, Sun QW. Effects of berberine on human rheumatoid arthritis fibroblast-like synoviocytes. Exp Biol Med 2011;236:859-66.
17. Fan D, Guo Q, Shen J, Zheng K, Lu C, Zhang G, *et al.* The effect of triptolide in rheumatoid arthritis: from basic research towards clinical translation. Int J Mol Sci 2018;19:376.
18. Ruan Q, Xu Y, Xu R, Wang J, Hua Y, Wang M, *et al.* The adverse effects of triptolide on the reproductive system of caenorhabditis elegans: oogenesis impairment and decreased oocyte quality. Int J Mol Sci 2017;18:464.
19. Zhang L, Wang T, Li Q, Huang J, Xu H, Li J, *et al.* Fabrication of novel vesicles of triptolide for antirheumatoid activity with reduced toxicity *in vitro* and *in vivo*. Int J Nanomed 2016;11:2663.
20. Wei ZF, Lv Q, Xia Y, Yue MF, Shi C, Xia YF, *et al.* Norisoboldine, an anti-arthritis alkaloid isolated from radix linderae, attenuates osteoclast differentiation and inflammatory bone erosion in an aryl hydrocarbon receptor-dependent manner. Int J Biol Sci 2015;11:1113.
21. Wei ZF, Lv Q, Xia Y, Yue MF, Shi C, Xia YF, *et al.* Norisoboldine, an anti-arthritis alkaloid isolated from radix linderae, attenuates osteoclast differentiation and inflammatory bone erosion in an aryl hydrocarbon receptor-dependent manner. Int J Biol Sci 2015;11:1113.
22. Duan C, Guo JM, Dai Y, Xia YF. The absorption enhancement of norisoboldine in the duodenum of adjuvant-induced arthritis rats involves the impairment of P-glycoprotein. Biopharm Drug Dispos 2017;38:75-83.
23. Luo Y, Wei Z, Chou G, Wang Z, Xia Y, Dai Y. Norisoboldine induces apoptosis of fibroblast-like synoviocytes from adjuvant-induced arthritis rats. Int Iimmunopharmacol 2014;20:110-6.
24. Fu Z, Chen Z, Xie Q, Lei H, Xiang S. Hesperidin protects against IL-1β-induced inflammation in human osteoarthritis chondrocytes. Exp Ther Med 2018;16:3721-7.
25. Wrubel KM, Riha PD, Maldonado MA, McCollum D, Gonzalez Lima F. The brain metabolic enhancer methylene blue improves discrimination learning in rats. Pharmacol Biochem Behav 2007;86:712-7.
26. Wei Guang YU, Yong SH, Jian Zhong WU, Yan Bing GA, ZHANG LX. Madecassoside impedes invasion of rheumatoid fibroblast-like synoviocyte from adjuvant arthritis rats via inhibition of NF-κB-mediated matrix metalloproteinase-13 expression. Chinese J Nat Med 2018;16:330-8.
27. Wang T, Wei Z, Dou Y, Yang Y, Leng D, Kong L, *et al.* Intestinal interleukin-10 mobilization as a contributor to the anti-arthritis effect of orally administered madecassoside: a unique action mode of saponin compounds with poor bioavailability. Biochem Pharmacol 2015;94:30-8.
28. Lu X, Zeng R, Lin J, Hu J, Rong Z, Xu W, *et al.* Pharmacological basis for use of madecassoside in gouty arthritis: anti-inflammatory, anti-hyperuricemic, and NLRP3 inhibition. Immunopharm Immunot 2019;41:277-84.
29. Wang T, Qiao H, Zhai Z, Tang T. Plumbagin ameliorates collagen-induced arthritis by regulating Treg/Th17 cell imbalances and suppressing osteoclastogenesis. Osteoarthr Cartil 2017;25:S417.
30. Fan H, Yang M, Che X, Zhang Z, Xu H, Liu K, *et al.* Activity study of a hydroxynaphthoquinone fraction from Arnebia euchroma in experimental arthritis. Fitoterapia 2012;83:1226-37.
31. Peres RS, Santos GB, Cecilio NT, Jabor VA, Niehues M, Torres BG, *et al.* Lapachol, a compound targeting pyrimidine metabolism, ameliorates experimental autoimmune arthritis. Arthritis Res Thera 2017;19:47.
32. Chen J, Wang Q, Wu H, Liu K, Wu Y, Chang Y, *et al.* The ginsenoside metabolite compound K exerts its anti-

inflammatory activity by downregulating memory B cell in adjuvant-induced arthritis. Pharm Biol 2016;54:1280-8.

33. Chen J, Wei W. Anti-arthritic effect and underlying mechanism of ginsenoside metabolite compound k. Clin Anti Inflamm Anti Allergy Drug 2015;2:47-51.
34. Zheng FL, Chang Y, Jia XY, Huang M, Wei W. Effects and mechanisms of cryptotanshinone on rats with adjuvant arthritis. Chinese Med J 2011;124:4293-8.
35. Wang Y, Wang S, Li Y, Jiang J, Zhou C, Li C, *et al.* Therapeutic effect of Cryptotanshinone on collagen-induced arthritis in rats via inhibiting nuclear factor kappa B signaling pathway. Transl Res 2015;165:704-16.
36. Yu Q, Wu J, Li Q, Jin L, Qu Y, Liang B, *et al.* Kirenol inhibit the function and inflammation of fibro-blast-like synoviocytes in rheumatoid arthritis *in vitro* and *in vivo*. Front Immunol 2019;10:1304.
37. Lu Y, Xiao J, Wu ZW, Wang ZM, Hu J, Fu HZ, *et al.* Kirenol exerts a potent anti-arthritic effect in collagen-induced arthritis by modifying the T cells balance. Phytomedicine 2012;19:882-9.
38. Lu Y, Xiao J, Wu Z, Wang Z, Fu H, Chen Y, *et al*. Effects of kirenol on bovine type II collagen-induced rat lymphocytes *in vivo* and *in vitro*. Nan Fang Yi Ke Da Xue Xue Bao 2012;32:1-6.
39. Faisal R, Ahmad N, Fahed YS, Chiragh S. Anti-arthritic effect of thymoquinone in comparison with methotrexate on pristane induced arthritis in female sprague dawley rats. J Ayub Med Coll Abbottabad 2018;30:3-7.
40. Faisal R, Shinwari L, Jehangir T. Comparison of the therapeutic effects of thymoquinone and methotrexate on renal injury in pristane induced arthritis in rats. J Coll Physicians Surg Pak 2015;25:597-601.
41. Arjumand S, Shahzad M, Shabbir A, Yousaf MZ. Thymoquinone attenuates rheumatoid arthritis by downregulating TLR2, TLR4, TNF-α, IL-1, and NFκB expression levels. Biomed Pharmacother 2019;111:958-63.
42. Fu X, Lyu X, Liu H, Zhong D, Xu Z, He F, *et al*. Chlorogenic acid inhibits BAFF expression in collagen-induced arthritis and human synoviocyte MH7A cells by modulating the activation of the NF-κB signaling pathway. J Immunol Res 2019. https://doi.org/10.1155/2019/8042097
43. Chen WP, Tang JL, Bao JP, Hu PF, Shi ZL, Wu LD. Anti-arthritic effects of chlorogenic acid in interleukin-1β-induced rabbit chondrocytes and a rabbit osteoarthritis model. Int Immunopharmacol 2011;11:23-8.
44. Chauhan PS, Satti NK, Sharma P, Sharma VK, Suri KA, Bani S. Differential effects of chlorogenic acid on various immunological parameters relevant to rheumatoid arthritis. Phytother Res 2012;26:1156-65.
45. Zheng Z, Sun Y, Liu Z, Zhang M, Li C, Cai H. The effect of curcumin and its nanoformulation on adjuvant-induced arthritis in rats. Drug Des Dev Ther 2015;9:4931.
46. Zahidah AF, Faizah O, Aqilah KN, Anna KT. Curcumin as an anti-arthritic agent in collagen-induced arthritic sprague-dawley rats. Sains Malays 2012;41:591-5.
47. Sumeet G, Rachna K, Samrat C, Ipshita C, Vikas J, Manu S. Anti inflammatory and anti arthritic activity of different milk based formulation of curcumin in rat model. Curr Drug Delivery 2018;15:205-14.
48. Mehwish M, Kanchan B. Evaluation of anti-inflammatory effect of pineapple juice in rheumatoid arthritis and osteoarthritis models in rats. Int J Med Health Sci 2015;4:70-6.
49. Kargutkar S, Brijesh S. Anti-rheumatic activity of ananas comosus fruit peel extract in a complete freund's adjuvant rat model. Pharm Biol 2016;54:2616-22.
50. Akhtar N, Haqqi TM. Current nutraceuticals in the management of osteoarthritis: a review. Ther Adv Musculoskelet Dis 2012;4:181-207.
51. Hidalgo MA, Hancke JL, Bertoglio JC, Burgos RA. Andrographolide a new potential drug for the long term treatment of rheumatoid arthritis disease. Hampshire, UK: InTech; 2013.
52. Li F, Li H, Luo S, Ran Y, Xie X, Wang Y, *et al.* Evaluation of the effect of andrographolide and methotrexate combined therapy in complete Freund's adjuvant induced arthritis with reduced hepatotoxicity. Biomed Pharmacother 2018;106:637-45.
53. Gupta S, Mishra KP, Singh SB, Ganju L. Inhibitory effects of andrographolide on activated macrophages and adjuvant-induced arthritis. Inflammopharmacology 2018;26:447-56.
54. Li ZZ, Tan JP, Wang LL, Li QH. Andrographolide benefits rheumatoid arthritis via inhibiting MAPK pathways. Inflamm 2017;40:1599-605.
55. Mandal SK, Das A, Dey S, Sahoo U, Bose S, Bose A, et al. Bioactivities of allicin and related organosulfur compounds from garlic: overview of the literature since 2010. Egypt J Chem 2019;62:1-11.
56. Rajagopala PL, Dhilnaa KK, Sajith Kumarb PN, Jeril J. Herbs in inflammation-a review. Int J Ayurvedic Herb Med 2013;3:1289–307.
57. Jayanthi MK, Naidu SV. Antioxidant and antiarthritic activity of allicin in animal models. Int J Pharm Sci Res 2015;6:1150-5.
58. Lin W, Hai Tao P, Bing W, Yang L, Kai F, Wei Feng H. Allicin reduces IL-1β-induced inflammatory cytokines via attenuating the NF-κB and MMP3 activation in human osteoarthritis chondrocytes model. Int J Clin Exp Pathol 2016:9;10320-26.
59. Gu X, Wu H, Fu P. Allicin attenuates inflammation and suppresses HLA-B27 protein expression in ankylosing spondylitis mice. Biomed Res Int 2013:1-6. https://doi.org/10.1155/2013/171573