

A Review on Beneficial Nutraceuticals for Arthritis

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ABSTRACT: Bone is a rigid and dynamic tissue. To carry out its functions efficiently, it is continuously remodeled and repaired. Arthritis is a chronic inflammatory joint disease that results from a change in control of pro-inflammatory enzymes that mediate production of prostaglandins, cytokines and leukotrienes. There is also a change in expression of adhesion molecules, matrix metalloproteinases and synovial fibroblasts hyper proliferation. All the above mentioned factors are regulated by the activation of NF- κ B. Thus those compounds that inhibit or suppress NF- κ B activation have the potential to be used in arthritis treatment. Many drugs have been developed for arthritis treatment but our main focus is on naturally derived products as the harmful side effects is the major problem associated with the NSAIDs. Numerous agents derived from plants, sponges etc. have been demonstrated to suppress these cell signaling intermediates. Plant products: curcumin (from turmeric), resveratrol (red grapes cranberries and peanuts) quercetin (onions), withanolides (ashwagandha) etc. have been discussed, focusing on the molecular target on which they act.. These small compounds are involved in inhibiting or accelerating the molecular mechanism that have been implicated in osteoclastogenesis.

KEYWORDS: Arthritis, autoimmune disease, inflammatory mediators, plant products, nutraceuticals.

I. INTRODUCTION

Bone is mainly composed of support cells i.e. bone forming osteoblasts (formed by the process of osteogenesis) and osteocytes; remodeling cells i.e. bone resorbing osteoclasts and non mineral matrix of collagen and non collageneous proteins called osteoid with inorganic mineral salts deposited in the matrix. The main bone remodelers are osteoclasts, osteoblast, osteoprotegerin, paracrine cell signaling and Receptor Activator of NF- κ B (RANK). Excessive formation of osteoclast causes diseases such as osteoporosis and rheumatoid arthritis. Arthritis is common chronic disorder that affects the joints. Bone remodeling is a natural process that occurs throughout life but only up to 50 years of age the balance is positive. From then on, resorption predominates leading to progressive decrease in bone mass, which goes on as age increases. As bone remodeling decreases post menopause and then slows down with further aging, women are more subjected to show rheumatoid arthritis (RA) symptoms in old age.

Although around 100 different forms of arthritis have been known till date, but we have mainly focused on Rheumatoid arthritis (RA) and Osteoarthritis (OA) which are the most common forms.

Osteoarthritis (OA) is result of articular cartilage failure which can be induced or is governed by following factors: metabolic, genetic, biochemical and biomechanical factors. Various drugs used in OA treatment include analgesics such as opioids and acetaminophen, NSAIDs, and intraarticular therapies like hyaluronans and glucocorticoids.

The local juxta-articular or periarticular osteoporosis is a well recognized phenomenon in Rheumatoid arthritis. About 75% women are RA patients, proving the role of hormones in the disease etiology. Exogeneous factors such as smoking and stress also contribute to RA which is characterized by stiffness and swelling in joints. The loss in flexibility is more evident in hip and radius than in spine. The main goal of RA treatment is to minimize swelling, pain,

delay disease progression and improve quality of life. In RA too, analgesics and intra articular therapies are used to control pain. Methotrexate (MTX), sulfasalazine, hydroxychloroquine, leflunomide and newer therapies such as tumor necrosis factor (TNF)- α therapy, anti-CD20 therapy and abatacept are used; but the main disadvantage with these therapies is that there are numerous side effects associated with these. This is the main reason because of which researchers are shifting their interest from synthetic to natural products that can modulate inflammatory process without causing harmful side effects. Rheumatoid arthritis (RA) is a chronic autoimmune disease. There is extensive inflammation of the synovial membrane which results in erosions of articular cartilage and marginal bone that leads to inflammation and joint destruction (Fig 1). Since arthritis is primarily a disease of joints and is a pro inflammatory disorder, thus a better understanding of the pro inflammatory nature of arthritis is essential if new therapies are to succeed.

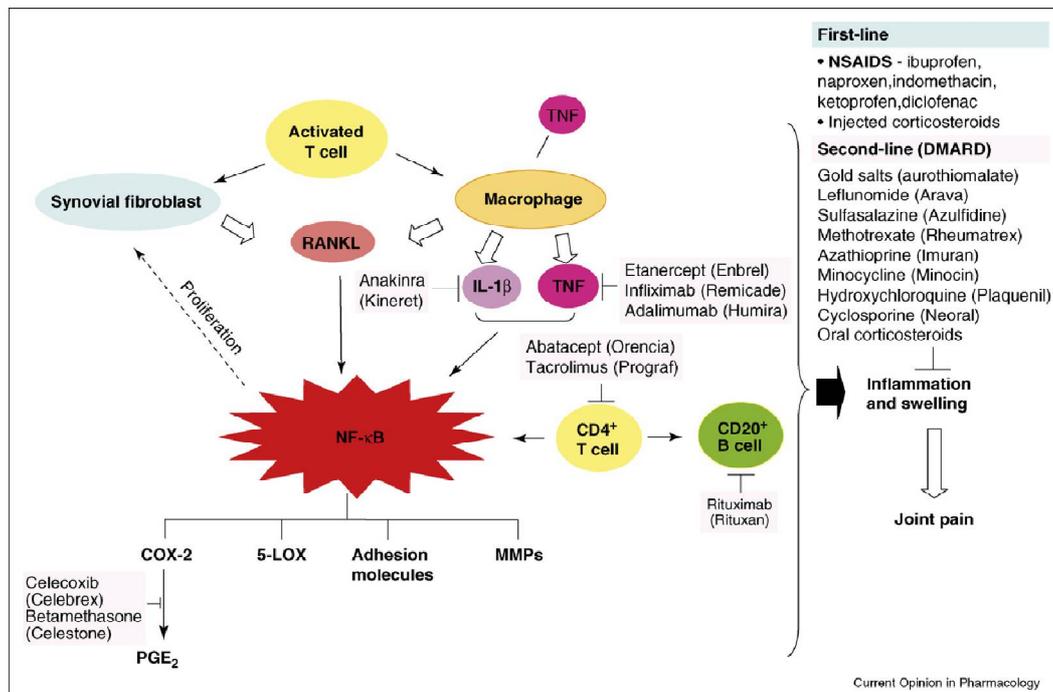


Fig1: Cell signalling network that mediates inflammatory response during arthritis and current therapeutic targets and their site of action.¹

A very complicated network of cytokines is involved in inflammation, which help in the perpetuation of rheumatoid arthritis by positive feedback, making it a systemic disorder. Endothelial dysfunction is also seen that is related to underlying chronic inflammation in rheumatoid arthritis².

The role of chemokines, inflammatory enzymes such as cyclooxygenase (COX)-2, 5-lipoxygenase (5-LOX) and matrix metalloproteinase (MMP)-9, interleukin (IL)-1b, IL-6, cytokines TNF- α and adhesion molecules in the pathogenesis of arthritis is well documented in literature³⁻⁶. Most of the inflammatory mediators involved in arthritis have been studied and shown to be regulated by nuclear factor- κ B (NF- κ B)⁶. Like most other autoimmune diseases, arthritis is more prevalent in the Western world than in other countries. Because current treatments employed for arthritis result in unwanted harmful side effects and are expensive, natural products devoid of such disadvantages offer a novel opportunity. Thus, the current review is a detailed discussion on potential of natural agents which can be used for arthritis treatment in future and present scenario.

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The word nutraceutical comes from the combination of two words: nutrition and pharmaceutical. It corresponds to food or food product that provides health and medical benefits, including prevention and treatment. By definition and regulatory laws they are devoid of adverse effects. Nutraceuticals are good candidates for long-term prevention of chronic disease, such as OA. There are several emerging alternatives. It is increasingly being recognized that nutraceuticals could help to maintain bone and joint health.

Agents derived from plants have potential of modulating the expression of pro-inflammatory signals against arthritis. The secondary metabolites involved in the anti-inflammatory process include flavanoids, terpenes, quinones, alkaloids, catechins, anthoxanthin and anthocyanin.

Some of these secondary metabolites (polyphenols) are discussed in this review and shown in table 1. Also the chemical structures of some natural compounds are shown in fig 2.

<u>Compounds</u>	<u>Source</u>	<u>Molecular targets</u>
• Boswellic acid	<i>Boswellia serrata</i> (Salai guggul)	NF-kB, COX-2, 5-LOX, MMP-9, ICAM-1
• Berberine	<i>Berberis vulgaris</i> (barberry)	NF-kB, COX-2, TNF-a, IL-1b, IL-6
• Celastrol	<i>Tripterygium wilfordii</i>	NF-kB, COX-2, MMP-9, TNF-a, AMs
• Cucurbitacin R	<i>Cayaponia tayuya</i>	NF-kB, COX-2, TNF-a
• Curcumin	<i>Curcuma longa</i> (tumeric)	NF-kB, COX-2, 5-LOX, TNF-a, IL-1b, IL-6, IL-8, MMPs, AM
• Eugenol	<i>Syzygium aromaticum</i> (cloves)	NF-kB, COX-2, 5-LOX, TNF-a, IL-1b
• Guggulsterone	<i>Commiphora mukul</i> (guggul)	NF-kB, COX-2, MMP-9
• Genistein	<i>Glycine max</i> (soybeans)	NF-kB, TNF-a, IL-1b, IL-6
• Luteolin	<i>Thymus vulgaris</i> (thyme)	NF-kB, COX-2, TNF-a
• Morin	<i>Chlorophora tinctoria</i>	NF-kB, COX-2, 5-LOX, MMP-9, TNF-a, IL-1b, IL-6
• Quercetin	<i>Allium cepa</i> (onions)	NF-kB, COX-2, TNF-a, 5-LOX, TNF-a, IL-1b, AMs
• Resveratrol	<i>Vitis vinifera</i> (red grapes)	NF-kB, COX-2, TNF-a, 5-LOX, AMs
• Rosmarinic acid	<i>Rosmarinus officinalis</i> (rosemary)	NF-kB, COX-2, TNF-a, AMs
• Silymarin	<i>Silybum marianum</i> (milk thistle)	NF-kB, COX-2, TNF-a, 5-LOX, AMs
• Statins	<i>Aspergillus terreus</i> (yeast)	NF-kB, COX-2, MMP-9, AMs
• Tea polyphenols	<i>Camellia sinensis</i> (black tea)	NF-kB, COX-2, TNF-a, 5-LOX, AMs, MMPs

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• Ursolic acid	<i>Ocimum sanctum</i> (holy basil)	NF-kB, COX-2, MMP-9
• Withanolides	<i>Withania somnifera</i> (Ashwagandha)	NF-kB, COX-2, MMP-9, ICAM-1

Table 1: Major natural products that can be used for treatment of arthritis.

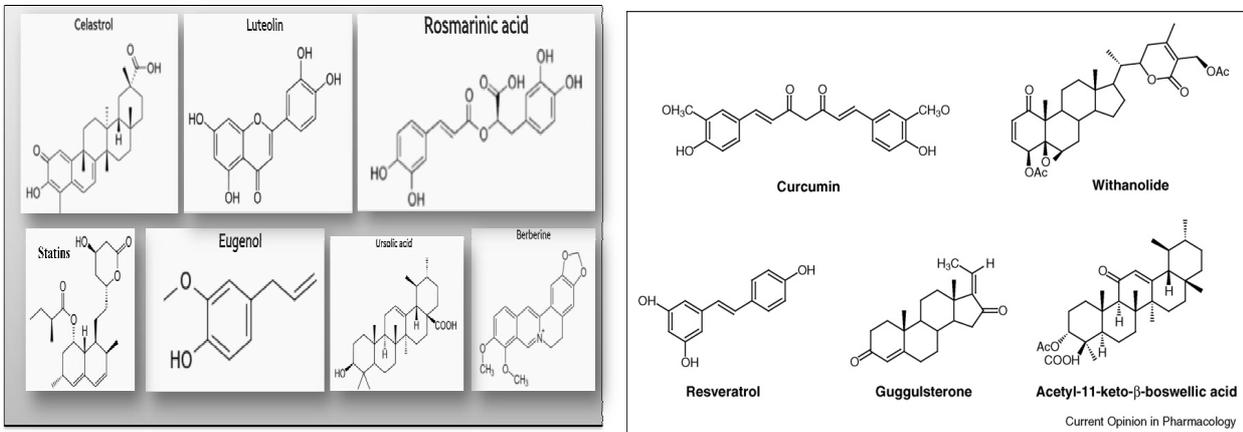


Fig 2: Structure of some natural compounds that can be used for treating arthritis

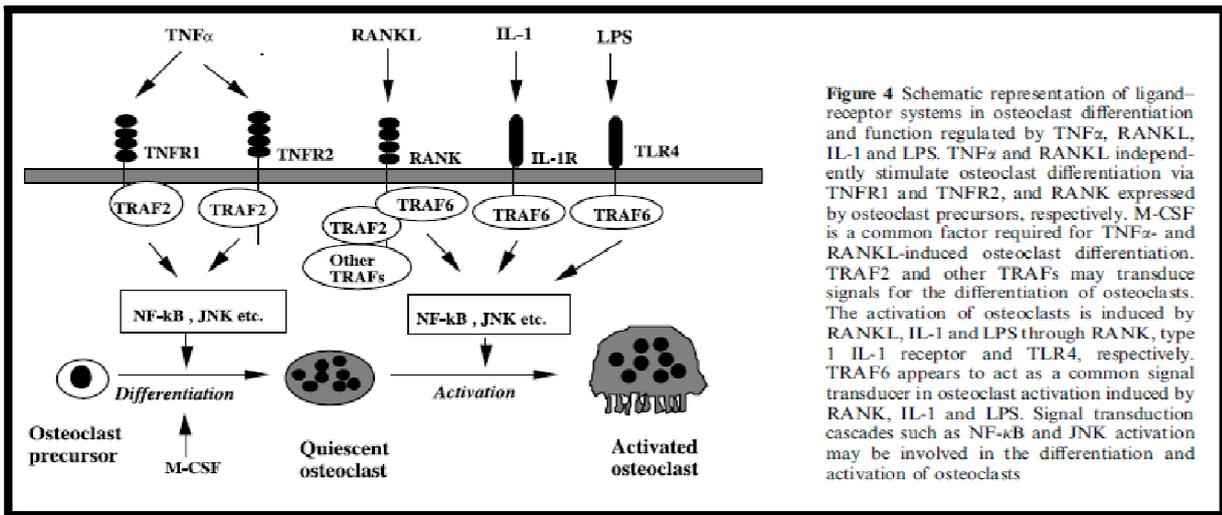


Fig 3: Major pathway in osteoclast differentiation. ⁸⁸

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II. NATURAL PRODUCTS THAT CAN BE USED IN ARTHRITIS TREATMENT

2.1 CURCUMIN (*Curcuma longa*)

Curcumin (diferuloylmethane), a yellow colouring agent is an active component of turmeric (*Curcuma longa*) has been used for centuries as a spice or condiment in India⁷. Curcumin has been well documented in Ayurveda as an anti-inflammatory, anti cancer, anti oxidant and antimicrobial agent⁸. Work from many laboratories have shown that curcumin has a potential of down regulating the NF-kB activation^{9,10}, further down regulating TNF- α expression^{9,11,12}, adhesion molecules¹³, matrix metallo proteinases (MMPs)¹⁴, COX-2¹⁵, lipoxygenase (5-LOX) genes¹⁵ and other inflammatory intermediates^{16,17}, all of which are associated with arthritis. Curcumin inhibits the upregulation of MMPs which are responsible for pathological features of RA such as degradation of cartilage^{18,19}. Curcumin also suppresses the TNF- α -induced MMP-13 expression in primary chondrocytes²⁰. It inhibits synovocyte proliferation, neutrophil activation, angiogenesis, stromelysin expression and regulates COX-2 inhibitor celecoxib in osteoarthritis synovial adherent cells^{20,21}. Recently it has been studied that inhibition of NF-kB activation by curcumin leads to inhibition of COX-2 and MMP-9 in human articular chondrocytes²². In vivo studies have shown that oral administration of curcumin decreases elevated levels of the glycoprotein GpA72, with lowering of paw inflammation in arthritic rats^{23,24}. The anti catabolic effects, namely reducing degradative enzyme activity, inhibiting IL-1 β binding and leading to inhibition of MMP (-), activating the collagen type II and increasing β 1 integrin suggests that it may be a suitable adjunct to conventional pharmaceutical therapy. Also, in contrast to NSAID, curcumin shows no signs gastrointestinal side effects. Therefore it could be beneficial in management of arthritis.

Table 2 summarizes the biological action of curcumin on joint tissues.

Biological actions of curcumin on joint tissues

Cell viability
-Decreases cell viability of adherent synoviocytes -No effect on cell viability of adherent chondrocytes, chondrocytes in alginate beads or in cartilage explants (at concentration below 30 mM) -Antagonizes IL-1b-induced caspase-3 activation in a time-dependent manner
Antioxidant effects
- Scavenger of reactive oxygen and nitrogen species in vitro - Inhibits IL-1b-induced NO production by bovine and human chondrocytes and human cartilage explants - Inhibits IL-1b-induced superoxide dismutase activity in bovine chondrocytes in monolayer
Anti-inflammatory effects
-Inhibits NF-kB-dependent gene transcription in chondrocytes -Inhibits COX-2, but not COX-1, gene expression in IL-1b-treated bovine chondrocytes in monolayer -Inhibits IL-6 and IL-8 gene expression by bovine and human chondrocytes -Inhibits IL-6, IL-8 and PGE2 production by human chondrocytes and cartilage explants
Anti-catabolic effects
-Inhibits IL-1b-induced glycosaminoglycan (GAG) release from canine and human OA cartilage explants - Decreases MMP-3 synthesis in chondrocytes in alginate beads and in human cartilage explants - Suppresses IL-1b and OSM-induced MMP-1, MMP-3, MMP-9 and MMP-13 gene expression by human chondrocytes via inhibition of NFkB activation and nuclear translocation
Anabolic effects
-No effect on aggrecan production by human chondrocytes in alginate beads - Decreases proteoglycan mRNA expression in bovine chondrocytes in monolayer - Reverses the IL-1b-induced inhibition of type II collagen and b1-integrin gene expression in human chondrocytes

Table 2: Biological action of curcumin on joint tissues.

Curcumin (C) has potential in preventing I κ B α phosphorylation, and translocation of active NF- κ B into the nucleus, further preventing it from activating MMPs gene expression, stimulators of MMP synthesis (like cytokines), inflammatory mediators (like cytokines and COX-2) and apoptotic executioners (like caspase-3). Fig 4 illustrates the potential sites of action of curcumin in the NF- κ B signaling pathway in a typical joint cell.

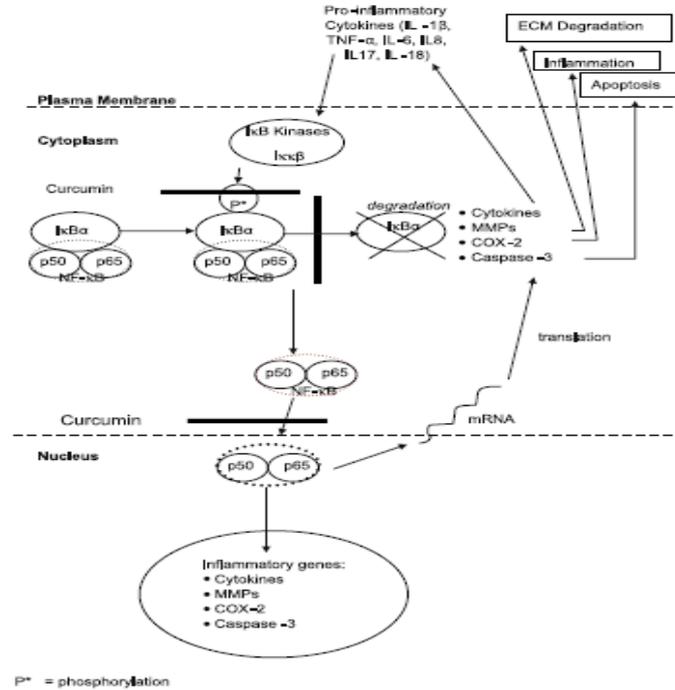


Fig 4: The curcumin/AP-1/NF- κ B axis in inflammatory cell signalling responses in joint cells.

2.2 RESVERATROL

Resveratrol is trans-3,5,40-trihydroxystibene. It was first isolated from *Veratrum grandiflorum* but later it was found as an active constituent of grapes, berries and peanuts²⁵. Research on the role of resveratrol has shown that it suppresses NF- κ B²⁶, COX-2, 5-LOX, IL-1b, and IL-6²⁷ which play important role in arthritis, and thus resveratrol may be used in treating OA and RA. Resveratrol also shows chondroprotective activities by increasing proteoglycan synthesis and chondrocyte proliferation and by suppressing IL-1, reactive oxygen species, p53-induced apoptosis, leukotriene B4, prostaglandin E2 synthesis and MMPs *in vitro* Tian et al. have showed that resveratrol suppresses the proliferation of synoviocytes, and induces caspase 3 mediated apoptosis *in vitro*²⁸. Resveratrol intra articular injections in OA experimental rabbits have shown to reduce cartilage tissue destruction suggesting that it can be used in arthritis treatment²⁸. However, additional clinical trials and *in vivo* studies are still needed. Recent studies have shown that although resveratrol induces fibroblast apoptosis but it also increases chondrocyte survival by activating Sirtuin 1 (a histone deacetylase) and Bcl2. Thus, it may be concluded that resveratrol may prevent OA-associated inflammation, intervertebral disc degeneration, chondrocyte apoptosis, and RA-related pannus formation.

Research has also been done on curcumin synergizing with resveratrol, stimulating the MAPK signaling pathway in human articular chondrocytes. Resveratrol potentiates curcumin antiapoptotic effect by blocking IL-1 β or U0126-induced inhibition of Erk 1/2 in chondrocytes as shown below in figure 5²⁹.

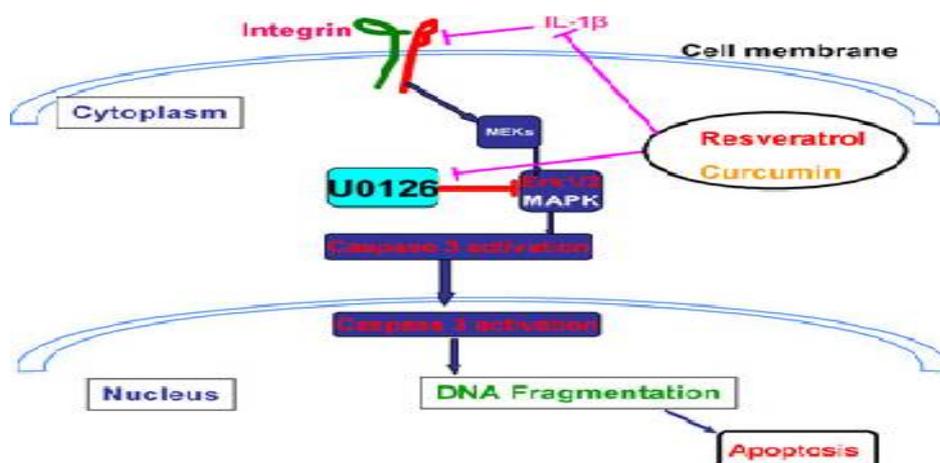


Fig 5: Molecular model outlining the proposed mechanism for the stimulatory effects of resveratrol and curcumin²⁹

2.3 BOSWELLIC ACID (*Boswellia serrata*)

Boswellic acid (BA) is an active component of *Boswellia serrata* (Salai guggul). *Boswellia serrata* is commonly found in India and is known for its guggulu(gum) that possesses anti-inflammatory, anti-arthritic, and anti-analgesic activity which further define its role in treatment of arthritis³⁰. It has been observed that the cytokines and inflammatory mediators TNF- α , IL-1 β and IL-6 are down regulated when peripheral blood mononuclear cells (PBMCs) are cultured in presence of methanolic extracts of *B. serrata*³¹

Extensive research has been carried out in the past 30 years that identified the active component of plant is 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 BSA induced arthritis³² and OA³³. NF-kB, COX-2 and 5-LOX are responsible for the anti-arthritic potential of BA. A randomized double blind placebo-controlled crossover study was conducted by Kimmatkar et al. to assess the efficacy, safety and tolerability of *B. serrata* extract in 30 patients with OA of the knee³³. During the study, 15 patients received 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. Patients receiving drug treatment reported a decreased knee pain, increased walking distance and increased knee flexion. Swelling in the knee joint was also decreased. *B. serrata* extract was well tolerated with minor gastrointestinal adverse reactions. *Boswellia carterii* when examined as an adjuvant had significant anti-arthritic and anti-inflammatory properties. It also significantly suppressed local tissue TNF- α and IL-1 β ³⁴. But further studies are still needed to understand its anti-arthritic potential. H 15 is a special extract of the gum resin of *B. serrata* that has been shown to be effective in rheumatoid arthritis (RA) treatment. The H15 extract has been shown decrease joint swelling, pain, erythrocyte sedimentation rate (ESR) with no side effects.³⁵

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2.4 GUGGULSTERONE (*Commiphora mukul*)

It is a gum resin derived from *Commiphora mukul*. It causes inhibition of NF-kB activation further leading to down-regulation of inflammatory gene product i.e. COX-2 and MMP-9 which are in turn involved in arthritis³⁶. The [4,17(20)-pregnadiene-3,16-dione] i.e. guggulsterone also suppress osteoclastogenesis induced by RANK-L.³⁷ Studies by Gujral et al. and Singh et al. have shown the anti arthritic effect of *C. mukul*^{37,38}. Gujral et al. compared the effect of anti inflammatory agent such as phenylbutazone, ibuprofen with guggulsterone action on rabbits resembling inflammatory symptoms similar to RA in humans, and found it to be effective as all the three compounds decreased joint swelling. Later both conducted preclinical and clinical investigation of gum and found that it reduces pain and stiffness, improved function and increases tolerability in older people who are diagnosed with OA. Thus, guggul appears to be safe and promising supplement to reduce OA symptoms.

2.5 WITHANOLIDES (*Withania somnifera*)

It is a potent inhibitor of angiogenesis, oxidative stress and inflammation. Anti arthritic potential of withanolide has been studied and it was concluded that it can inhibit the NF-kB activation and its gene regulation.^{39,40} The long term effect of withanolide on adjuvant induced arthritic rats was first shown by Begam and Sadique⁴¹. Rasool and Varalakshmi recently studied the effect of *W. somnifera* root powder on paw volume and serum lysosomal enzyme activities in rats in which arthritis was induced by monosodium urate crystal⁴². In MSU treated rats the β -glucuronidases and lactate dehydrogenase activity increased but when these rats were treated with withanolide the activity of these enzymes reverted back to normal. This illustrates the potent analgesic and antipyretic effect, which further provide evidence for withanolide's anti arthritic effect by reducing inflammatory response and gastric damage.

2.6 GENISTEIN (*Glycine max*)

Genistein is an isoflavonoid and active component of soya bean (*Glycine max*). As stated earlier the symptoms of arthritis are more pronounced in menopausal and post menopausal women. Genistein a phytoestrogen has been studied in vitro ; although its role in arthritis is not yet clear but it acts as an anti inflammatory agent suppressing COX2, NF-kB, 5-LOX, TNF- α and IL-1b⁴³.

2.7 NIGA-ICHIGOSIDE F₁ and 23-HYDROXYMENTIC ACID (*Rubus coreanus*)

The triterpenoid glycoside niga-ichigoside F₁ (NIF₁) and its aglycone 23-hydroxytormentonic acid (23-HTA) are isolated from the unripe fruit of *Rubus coreanus* (Rosaceae). Chemically, NIF₁ and 23-HTA were studied as Freund's complete adjuvant – induced edema of the hind paw in rats and shown in the table 4. It is well established that the triterpenoids and saponins reduce ROS levels in RA model⁴⁴.

GROUP	DOSE(mg/Kg)	RA	CRP
Untreated	-	-	-
Control	-	10	10
NIF1	10	8	9
	30	7	7
23-HTA	10	6	7
	30	4	3
Methyl prednisolone	10	3	2

Table 4: Inhibitory Effect of Niga-ichigoside F1 and 23-Hydroxytormentonic Acid on Freund's Complete Adjuvant-Induced Edema of the Hind Paw in Rats; C-reactive protein being the diagnostic index.

RA factor is positive in 80% of RA patients and C-reactive protein (CRP) is the diagnostic index that gives an idea of bacterial infection, RA, RA fever, suppurative arthritis, malignant tumor and gout. FCA treated rats produce considerably high amounts of RA and CRP. The two compounds, NIF1 or 23-HTA, and a standard drug, MTP (the

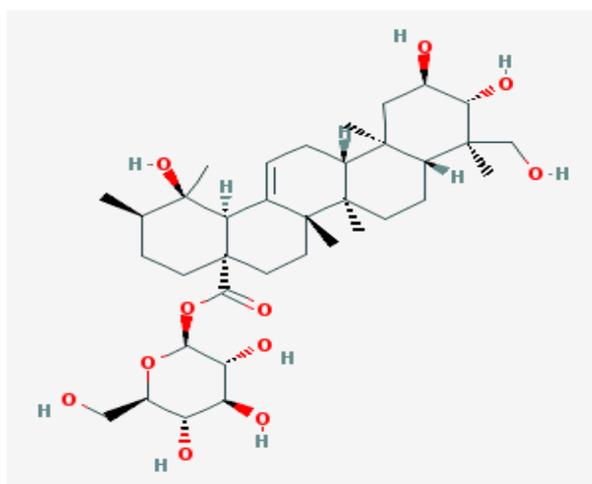
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positive standard), reduced these factors, suggesting that these compounds are effective against the rheumatic disease. 23-HTA exhibited a more pronounced effect than NIF1. Thus it can be concluded that the NIF-1 and 23-HTA compounds have an anti-rheumatic effect.



2.8 ANDROGRAPHOLIDES

Andrographolides (AP) comprise of 70% plant extract. It is a labdane diterpenoid which is isolated from traditional Chinese and Indian medicinal plant *Andrographis paniculata*. AP suppresses the osteoclastogenic cytokine i.e. RANK-L mediated osteoclast differentiation bone resorption (invitro) and reduces expression of osteoclast specific markers such as tartarate resistant acid phosphatase, calcitonin receptor and cathepsin K. Andrographolide induces arrest of cell cycle and apoptosis in human rheumatoid arthritis fibroblast-like synoviocytes⁴⁵. Andrographolides also promote the development of regulatory T cells thereby to ameliorating rheumatoid arthritis by⁴⁶. Like curcumin, AP too exhibits anti inflammatory, anti cancer and hepatoprotective activities⁴⁷.

Osteoclast formation depends on several factors including Macrophage colony stimulating factor (MCSF) and RANK-L. AP presence in the cell inhibits the covalent modification of cysteine on p50 in endothelial cells⁴⁸. According to above finding, Zhai et al hypothesized that AP may represent a novel treatment for osteoclast related osteolytic diseases⁴⁹. The effect of AP can be seen in the figure 6.

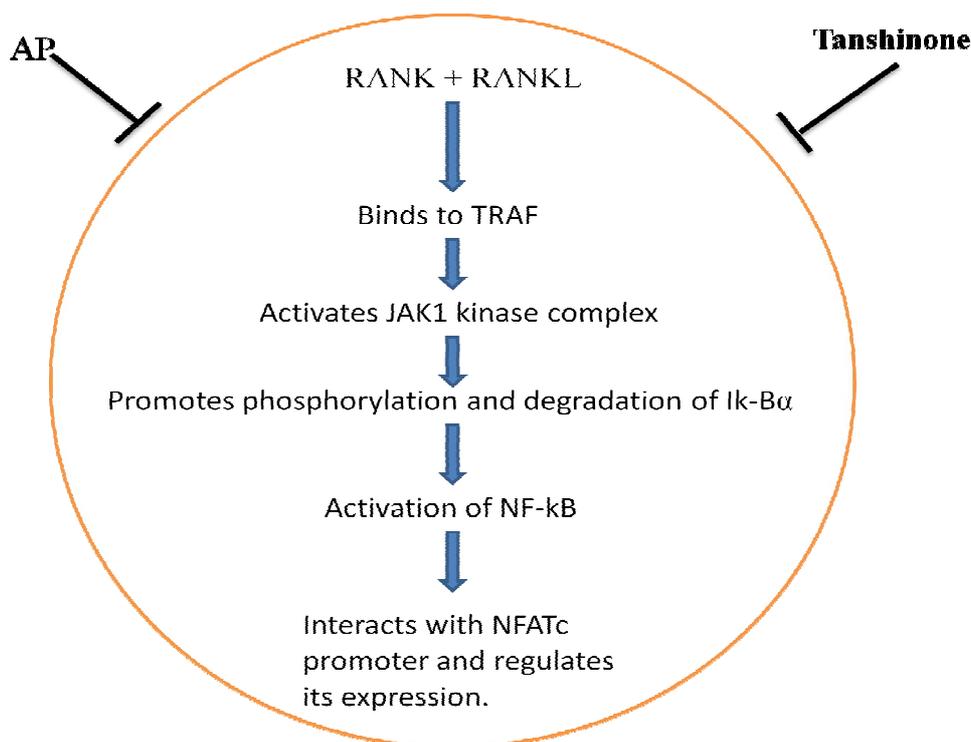


Fig 6: Inhibition of RANKL activated NF-kB activation

2.9 METHANOLIC EXTRACT from *Payena dasyphylla*

Payena dasyphylla is a Malaysian plant from which 20 methanolic crude extracts from ten different parts have been screened which contain phenols and flavanoids having antioxidant, anti-inflammatory, anti-atherosclerotic, anti-carcinogen and anti-apoptotic properties have been isolated. The methanolic extract is extracted from bark and leaf which are effective against both hyaluronidases and MMPs (Matrix Metalloproteinases). Researchers took ethyl acetate fraction of *P. dasyphylla* and tested to evaluate its anti hyaluronidase activity by inhibiting HYAL-1 and HYAL-2 gene expression and the inhibiting effect is seen on MMPs--- MMP3 which degrades matrix component leading to cleavage of collagen and proteoglycans, and MMP13 which degrades type II collagen.⁵⁰

Citalingam et al⁵⁰ have estimated that 100µg/ml of *P. dasyphylla* possesses 82.19% antioxidant radical scavenging activity. As reactive oxygen species (ROS) promote cartilage destruction thus, inhibition of these ROS restore and maintain articular cartilage from further destruction in OA.

2.10 QUERCETIN (*Allium cepa*)

Quercetin is a plant flavanoid extracted from onion as well as from fruits, and is well known for its anti inflammatory property. Studies on quercetin have shown that it is a potent anti-inflammatory agent⁵¹. It acts by inhibiting TNF-α mediated IL-8 and expression of monocyte chemoattractant protein-1 (MCP-1). Quercetin inhibits production of inflammation-producing enzymes (cyclooxygenase (COX) and lipoxygenase (LOX)⁵². Quercetin also has an inhibitory effect on iNOS expression and NF-κB activation. Moreover, it inhibits LPS-induced STAT-1 activation. This

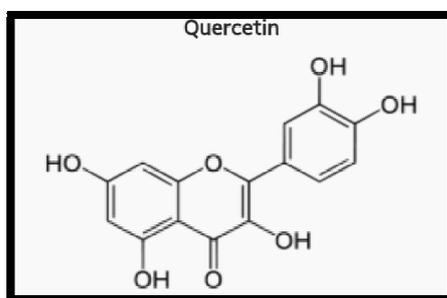
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inhibition of STAT-1 activation by quercetin is most likely involved in the mechanisms by which quercetin inhibits iNOS expression, because JAK inhibitors AG-490 and WHI-P154 have been shown to inhibit iNOS expression along with their suppressive actions on STAT-1 activation⁵³. Quercetin has been seen to reduce the expression of human CRP and cardiovascular risk factors (SAA, fibrinogen) in mice *in vivo*. These systemic effects together with local anti-proliferative and anti-inflammatory effects in the aorta may contribute to the attenuation of atherosclerosis⁵⁴. This suggests quercetin to be a potent anti-arthritis agent but further preclinical trials are still needed.



2.11 VENTOL (*Ecklonia cava*)

Ventol, a phlorotannin is an anti-oxidant and anti-inflammatory substance. *Ecklonia cava* is edible marine brown algae with a number of phlorotannins with beneficial activities. An *in-vitro* study has shown that ventol inhibits proteoglycan degradation after IL-1 α stimulation which may suggest it to be anti-OA but studies are needed to confirm it as potent anti-arthritis⁵⁵. Ventol significantly down regulates the generation of PGE₂ in LPS-treated RAW 246.7 cells. It also inhibits human recombinant interleukin-1 α -induced proteoglycan degradation, indicating its beneficial involvement in pathophysiological consequences of osteoarthritis⁵⁵. Phlorotannin-rich extracts of *Ecklonia cava* show significant antioxidant activities such as DPPH radical scavenging, ferric ion reduction, peroxynitrite scavenging, and inhibition of LDL oxidation, indicating their possible antioxidative interference both in onset and downstream consequences of osteoarthritis⁵⁶. Phlorotannin-rich extracts of other *Ecklonia* species also have considerable anti-inflammatory activities and are thus used as potential anti arthritic nutraceuticals⁵⁷.

2.12 PRODELPHINIDINS

Prodelphinidins and procyanidins are class of tannins which are composed of gallo catechin and epigallocatechin that occur naturally in grapes. Osteoarthritis is the clinical expression of the loss of cartilage function. COX inhibitors are widely used in the treatment of such pathologies for their beneficial effects on inflammation but often produce a negative activity on cartilage synthesis. *In vitro* study has shown its effect on human chondrocytes. Prodelphinidins inhibits PGE₂ synthesis by inhibiting COX2⁵⁸ and increase PG and type II collagen. Studies suggest that the prodelphinidins fractions from *R. nigrum* may be useful as an additive agent in the prevention of osteoarthritis. But further studies and clinical trials are needed to confirm it as potent anti-arthritis agent⁵⁸. Procyanidins too are known to exert anti-inflammatory effects and can thus be used to alleviate symptoms of arthritis⁵⁹.

2.13 TEA POLYPHENOLS (*Camellia sinensis*)

Research on polyphenols has shown to strongly support its role in prevention of degenerative diseases. Epigallocatechin-3-gallate (EGCG) is the major component of polyphenolic fraction of *Camellia sinensis* and is shown to exhibit anti-oxidant, anti-tumor and anti-mutagenic activities. Beneficial health effects of green tea that are supported by epidemiological and experimental studies include the inhibition of tumor formation and growth and inhibition of the development of collagen-induced arthritis in mice. A polyphenolic fraction from green tea that is rich in antioxidants may be useful in the prevention of onset and severity of arthritis⁶⁰.

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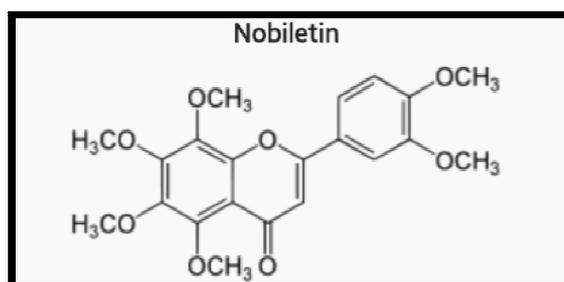
In vitro studies on human chondrocytes have demonstrated the anti-inflammatory effect of epigallocatechin-3-gallate by inhibiting the production of key inflammatory mediators i.e. NO, PGE₂, iNOS and COX-2^{61,62}. Anti inflammatory effect is observed by inhibition of IL-6 in osteoblast⁶³ and inhibition of COX-2 expression and synthesis and by PGE₂ inhibition and IL-8 secretion in synovial fibroblast. EGCG acts in a dose dependant fashion and is seen to significantly suppress COX-2 upregulation in synovial fibroblasts induced by IL-1 β . PGE₂ and IL-8 secretion was also induced by IL-1 β stimulation and significantly suppressed by EGCG. The mechanism is associated with the phosphorylation of IKK β . EGCG may inhibit the expression of inflammatory mediators, such as COX-2, PGE₂, and IL-8, induced by IL-1 β in human synovial fibroblasts. Thus EGCG may be of value in the treatment of synovial inflammation⁶⁴. Also EGCG shows additional anti-inflammatory and anti catabolic effect. EGCG has been shown to inhibit TNF- α and MMP-13 production induced by AGEs (Advanced Glycation End products) that are responsible for cartilage mechanical properties loss. It is interesting to note that the tea phenolic fraction might be involved in the inhibition of NF- κ B signaling and MAPK pathway, thus preventing the onset of arthritis and severity of disease. The anti-rheumatic activities of epigallocatechin-3 gallate (EGCG), a potent anti-inflammatory molecule found in green tea have been studied and EGCG may be tested for its potential anti-rheumatic beneficial activity in animal models of human RA⁶⁵.

3.14. PYCNOGENOL (*Pinus pinaster*)

Pycnogenol is extracted from the bark of *Pinus pinaster*. It is a concentrate of polyphenols, phenolic acids, taxifolin, procyanidins and catechin. Pycnogenol is known for its anti-oxidant, anti-inflammatory and inhibitory effect on MMPs and iNOS⁶⁶. Although the studies on pycnogenol effect in knee OA patients indicated that its daily intake of 150 mg alleviated OA symptoms^{66,67} but the studies also showed that the physical function and stiffness was improved by Pycnogenol intake of in OA subjects also it reduced NSAIDs or COX-2 inhibitor medication, suggesting that it can be used an effective adjuvant treatment. Treatment of cells with pycnogenol inhibits the release of ROS; ROS play an important role in inflammation, contributing to injury and degenerative processes like cartilage degradation in arthritis^{68,69}. Pycnogenol thus offers an option for reduction of treatment costs and side effects by sparing antiinflammatory drugs⁷⁰.

2.14 NOBILETIN

Nobiletin is a flavonoid isolated from citrus peels. It is a polymethoxyflavone that prevents cancer and inflammation, In vivo and in vitro studies in synovial fibroblast and articular chondrocytes have confirmed anti-inflammatory, anti-tumor proliferative, invasive and metastasis nature of nobiletin. The compound is able to inhibit mediators of inflammation like (PGE₂) and production of catabolic factors (MMP-3,-9 and ADAMTS-4, -5, a disintegrin and metalloproteinase with thrombospondin motifs), and activate the MMP inhibitor (TIMP-1, tissue inhibitor of metalloproteinases) in rabbit and human synovial fibroblasts^{71, 72}. Nobiletin suppresses IL-1-induced osteoclast formation by inhibiting NF κ B-dependent PGE₂ production in osteoblasts. Nobiletin also restores bone loss due to estrogen deficiency; hence the intake of nobiletin rich citrus fruits or a nutritional supplement may be beneficial for maintaining bone mass in postmenopausal women⁷³. Thus it can be safely said that the nobiletin demonstrates the potential to inhibit cartilage degradation.



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2.15 TANSHINONE VI (*Salvia miltiorrhiza*)

Tanshinone is a diterpenoid that is extracted from the roots of *Salvia miltiorrhiza* bunge (Labiatae). It is a Chinese traditional crude drug referred to as Tan-shen. It is widely used in prevention of cardiac disease, arthritis and other inflammatory diseases. The actual role of this tanshinone VI-A in osteoclast-related bone disease is not known till date. However,

tanshinone is found to inhibit osteoclast differentiation and suppress bone resorption through disruption of actin ring. It prevents osteoclast differentiation by inhibiting RANKL (Receptor activator of nuclear factor kappa-B ligand) expression and inhibiting activation of NF- κ B. In an experiment performed by Nicolin, tanshinone was extracted with ethanol-n-hexane which when co cultured in the bone marrow model of cells (3D osteoblast), the expression of RANKL and levels of NF- κ B decreased suggesting that tanshinone -VI may affect RANKL induced signaling involved in osteoclastogenesis⁷⁴. It has thus been hypothesized that “Pharmacological suppression of NF- κ B and RANKL is induced by tanshinone-VI which may be an effective approach to improve bone loss suppressing osteoclastic bone resorption.”⁷⁵

2.16 TANSHINONE II A (*Salvia miltiorrhiza*)

Diseases such as osteoporosis and rheumatoid arthritis are caused by excessive osteoclast formation. Work done by Kwak et al has shown that there is an inhibitory effect of tanshinone IIA on osteoclast differentiation, suggesting that tanshinone IIA may have a role as a therapeutic drug in the treatment of bone disease such as osteoporosis⁷⁵. Tanshinone II A that is extracted from *Salvia miltiorrhiza* inhibits receptor activator for NF- κ B ligand (RANKL) mediated osteoclast differentiation of osteoclast precursors. The expression of c-Fos induced by RANKL plays an essential role in initiation of osteoclast differentiation. As NFATc1 can induce osteoclast differentiation in the absence of RANKL thus it proves to be essential factor in osteoclast differentiation⁷⁶. Kim et al. too have shown that tanshinone II A inhibits osteoclast differentiation and suppresses bone resorption through actin ring disruption⁷⁷. Tanshinone II A prevents osteoclast differentiation by inhibiting c-Fos and NFATc1. As NFATc1 is expressed in osteoclast precursor through Ca^{+2} oscillation and c-Fos in response to RANKL which is required for the regulated expression of many genes, including TRAF6 (TNF receptor associated factors), calcitonin receptor and cathepsin K⁷⁶. Thus regulation of NFATc1 expression in osteoclasts precursors has significant consequences for bone disorder therapeutics concluding that tanshinone II A prevents functional cooperation between NFATc1 and NF- κ B in response to RANKL.

2.17 HONOKIOL (*Magnolia officinalis*)

Honokiol ($\text{C}_{18}\text{H}_{18}\text{O}_2$) is a biphenolic compound purified from the bark of *Magnolia officinalis*, a plant used in traditional Chinese medicine with minimal side effects. Honokiol has been shown to possess effect of anti-oxidation, against lipid peroxidation and anti inflammation in vitro and in vivo. It is also shown that honokiol down regulated the translocation of NF- κ B by inhibiting the upstream kinases like I κ B kinase, a critical step in early inflammatory responses. Although the effect of honokiol on chondrocytes is still unclear, but in the study by Ying ju Chen et al. it was concluded that honokiol exerts an anti-inflammatory effect by inhibiting COX-2/PGE₂ and iNOS/NO expression / production, IL-6 and MMP-13 production, and collagen II reduction via IKK/I κ B α /NF- κ B signaling inhibition as shown in Fig 7⁷⁸

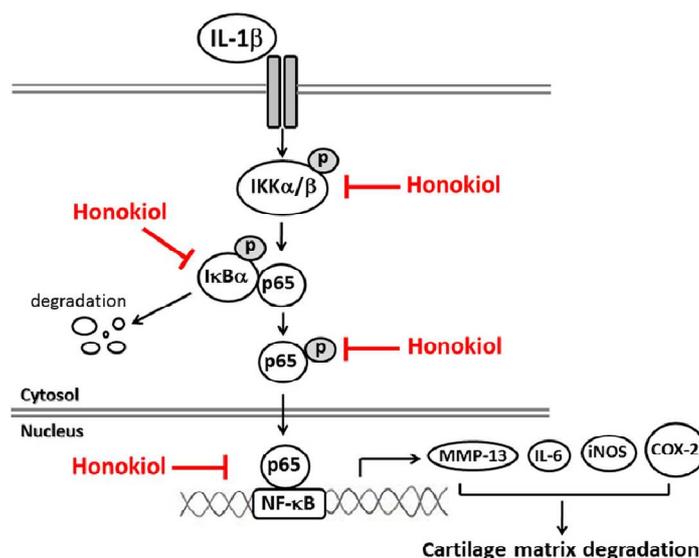


Fig 7: Inhibition at various sites by honokiol causing anti-inflammatory response⁷⁸

2.18 HERBAL LEUCINE MIX (HLM)

Herbal leucine mixture is a mixture of extract from three plants *Uncaria tomentosa*, *Lepidium meyenii*, *Boswellia serrata* and L-leucine. The *Boswellia spp.* is native to Ethiopia, India, Somalia and Arabian peninsula and it produces olibanum (frankincense) i.e. gum resin. Boswellic acid extracted from the plant, is widely used in the treatment of RA and other inflammatory diseases. *Lepidium meyenii* (maca) is Andean plant and belongs to Brassicaceae and is found to be chondroprotective which is mediated by upregulating IGF-1 expression even in IL-1 cytokine presence. When *Lepidium meyenii* is combined with *Uncaria guinensis* (cat claw) the cartilage breakdown is prevented and the balance of genetic resources governing metabolism and catabolism is maintained and enhanced in human cartilage⁷⁹.

Cats claw is an Amazonian vine, the bark of which is used to manage inflammation including joint health. Also the branched chain amino acid Leucine used serves as both substrate and stimulating signal for protein synthesis through mTOR signaling pathway.

The herbs in combination used proved to be strong beneficial factor with no or minimal undesirable effects instead play curative role.

According to Nahid Akhtar et al., HLM may serve as anti-inflammatory or chondroprotective agent, switching chondrocytes gene expression from catabolic direction to regenerative and anabolic and consequently this approach may be potentially useful as a new adjunct therapeutic agent for OA or injury recovery⁷⁹.

Thus the effect of HLM is studied in expression of key molecules that are believed to be involved in OA pathogenesis such as NO, COL2A1 (collagen type II alpha 1 chain), ACAN (aggrecan), GAG (glycosaminoglycan) and MMPs in human OA chondrocytes and cartilage explants stimulated with IL-1β.

2.19 HYMENIALDISINE

Hymenialdisine is a natural product isolated from marine sponges *Axinella verrucosa* and *Acanthella aurantiaca*⁸⁰. This compound has been shown to inhibit IL-8, NF-κB mediated IL-1β-stimulated prostaglandin E₂ production in human macrophages cell line and in human rheumatoid synovial fibroblasts respectively. Badger et al.⁸¹ showed that hymenialdisine inhibits retinoic acid induced stimulation of proteoglycan release and IL-1 stimulated NO production.

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These anti-inflammatory effects in cartilage may be because the compound inhibits PTK (protein tyrosine kinase) which further suggests that it might show beneficial effects in the treatment of RA and / or OA.⁸¹

2.20 WIN 34 B

WIN-34B is an extract prepared from a mixture of dried *Lonicera japonica* (Japanese honeysuckle) flowers and *Anemarrhena asphodeloides* root on the basis of extensive clinical experiences and experimentation demonstrating excellent anti-nociceptive and anti-inflammatory properties. Similar effects on animal model and in vitro evidence of cartilage protection and anti-inflammatory properties on the basis of preliminary data have been reported^{82,83}. Both *Lonicera japonica* and *Anemarrhena asphodeloides* root are traditionally used in Eastern medicine to treat inflammatory diseases. *Lonicera japonica* has properties like anti-angiogenic, anti-nociceptive, and anti-inflammatory effects⁸⁴. Also in vivo testing has shown that there are no side effects observed on administration of WIN34B⁸². In addition to anti-inflammatory effects *Anemarrhena asphodeloides* also exhibits antifungal and antiviral activities^{85, 86,87}. It has been recently reported that WIN-34B have analgesic and anti-inflammatory effects equal or superior to those of diclofenac and celecoxib in an in vivo model, suggesting it can be used as a new medication for OA⁸².

III. CONCLUSION

Arthritis particularly Osteoarthritis (OA) and Rheumatoid Arthritis (RA) are debilitating chronic diseases for which alternative treatment is must that could be beneficial to patients in long run preserving their joint function and therefore maintain their life quality. In the review we have used text-mining and a conventional literature search to summarize the research that has been done till date. Although the majority of papers quoted in this review may support the scientific rationale that the natural compounds benefits arthritic patients, but much more research is needed to understand better specially its potential side effects and contra-indications associated with long-term consumption. This review also highlights the fact that the effects of compounds are relatively limited. However, the existing published research suggests that it may aid to prevent or delaying the onset of arthritis. It has been found that the compounds are powerful inhibitor of inflammatory mediators, indicating that they could be an alternative to NSAIDs. In contrast to NSAIDs, the compounds have no gastrointestinal side effects, and it can even protect the gastric mucosa. Therefore, nutraceuticals could be beneficial in the management of chronic inflammatory-related joint disease, including OA and RA. However, despite this optimistic view, it must be recognized that there is a paucity of data regarding possible adverse effects of compounds at concentrations that are biologically effective in vitro.

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