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Review Article

Receptor Tyrosine Kinase (RTKs) Mediated Potent Bioactive Ligand Targeted to Autoimmune Arthritis

Nikita Patel [1], Trilochan Satapathy *, Poonam Sahu, Pratibha Dhiwar, Kamaksha Tiwari, Laxmi Sahu

Columbia Institute of Pharmacy, Village Tekari, Near Vidhansabha, Raipur-493111, C.G., India.

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*Address for Correspondence:

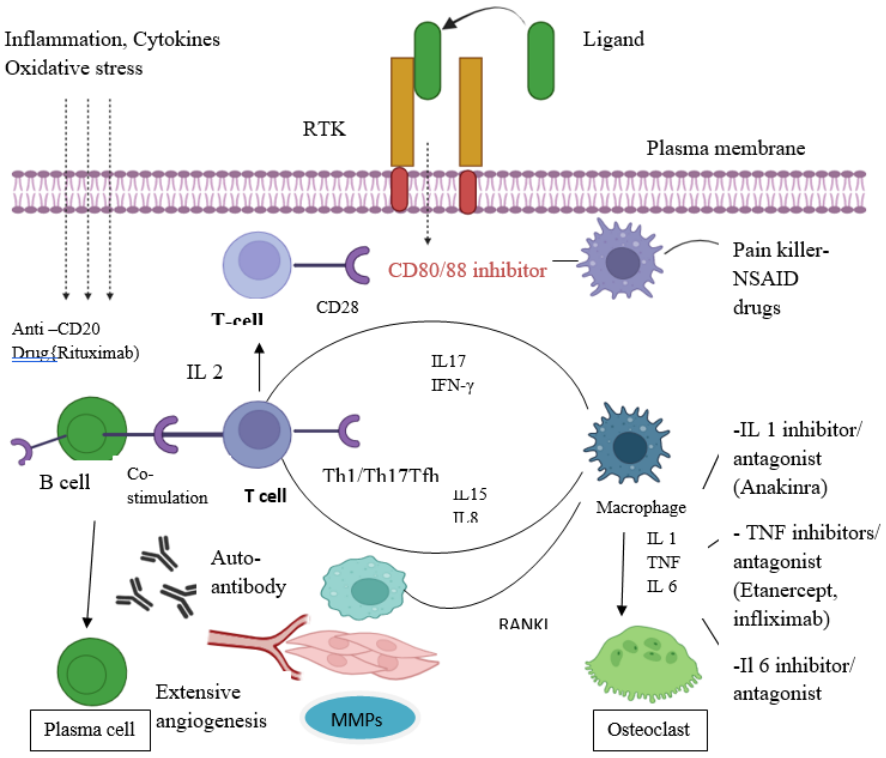
Dr. Trilochan Satapathy, Professor and HOD, Columbia Institute of Pharmacy, Tekari, Near Vidhansabha, Raipur-493111, Chhattisgarh, India

Abstract

This review aims to explore the Pharmacological potential of some important bioactive targets linked to Receptor Tyrosine Kinase (RTK) receptors in autoimmune arthritic disorders. RTKs play a role in inflammation, immune cell activation, angiogenesis, cartilage degradation, and autoantibody formation. Focusing on these pathways will pave the way for establishing a new treatment option for diseases such as rheumatoid arthritis. In conditions like autoimmune arthritis, inflammation results from immune cells such as T cells, B cells, and macrophages becoming activated and infiltrating the joints. The signaling of several immune receptors, including the TNF and IL-1 receptors, which are considered as important mediators of inflammation, is mediated by RTKs. Herbal bioactives are considered safer than other systems of medicine and possess outstanding therapeutic potential. In this review, we have considered some crucial bioactives that interact with RTKs to modulate their signaling pathways to be helpful for the treatment of various autoimmune disorders like rheumatoid arthritis, etc.

Keywords: Receptor Tyrosine Kinase, herbal bioactive, therapeutic potential, autoimmune disorder, rheumatoid arthritis, inflammation

Graphical abstract



1. Introduction:

A class of inflammatory joint illnesses known as autoimmune arthritis occurs when the body's own tissues, especially the joints, are mistakenly attacked by the immune system [1]. Chronic inflammation, discomfort, and joint degeneration are the results of an immunological reaction [2]. Among the different kinds of autoimmune arthritis, the rheumatoid arthritis (RA) is the most prevalent. The World Health Organization (WHO) estimates that up to 355 million people worldwide suffer with arthritis [3]. Millions of people are impacted globally, caused by a variety of elements, such as illness, injury, heredity, and the immune system. The cause depends on the type of arthritis like Osteoarthritis (OA), Rheumatoid Arthritis (RA), Psoriatic Arthritis, Gout, and Juvenile Idiopathic Arthritis (JIA) [4]. This condition arises due to wear and tear (degenerative changes), infections, genetic factors, metabolic disorders, lifestyle and environmental Factors. According to statistics, the prevalence of arthritis in American countries range is 21.2% of U.S. adults (53.2 million people), while in European countries ranges from 0.29% to 0.57% [5].Conventional treatments for autoimmune arthritis, including corticosteroids, disease-modifying anti-rheumatic medications (DMARDs), and non-steroidal anti-inflammatory drugs (NSAIDs), can be useful in controlling symptoms and delaying the course of the condition, but they also have a number of drawbacks and possible adverse effects [6]. Long-term usage of NSAIDs (such as naproxen and ibuprofen) can have varying effects on different organs [7]. These can aggravate the lining of the stomach resulting in gastric ulcers and bleeding, kidney strain that may cause kidney damage or diminished kidney function, increased risk of heart attack or stroke especially in those with pre-existing heart conditions as well as affect liver function in certain individuals resulting in elevated liver enzymes and possibly causing liver damage[8]. Similarly, corticosteroids enhance fluid retention, resulting in considerable weight gain and swelling. Their use for an extended period can weaken bones, raising the risk of fractures, and weaken the imm une system, leaving people more vulnerable to infection s[9]. These restrictions frequently lead to the pursuit of more specialized or alternative treatments. Bioactive substances found in a variety of plants have been found to interact with Receptor Tyrosine Kinases (RTKs), preventing their over activation and lowering the inflammation and accelerating the healing process [10]. Substances like resveratrol (found in grapes), curcumin (found in turmeric), and epigallocatechin gallate (EGCG) (found in green tea) have demonstrated encouraging results in inhibiting signaling pathways linked to RTK [11]. These substances can lower oxidative stress, inhibit pro-inflammatory cytokines, and shield cartilage from deterioration-all of these are essential for regulating the course of arthritis. Herbal bioactive that target RTKs may provide a safer, more natural substitute or supplement of traditional medication therapy [12].

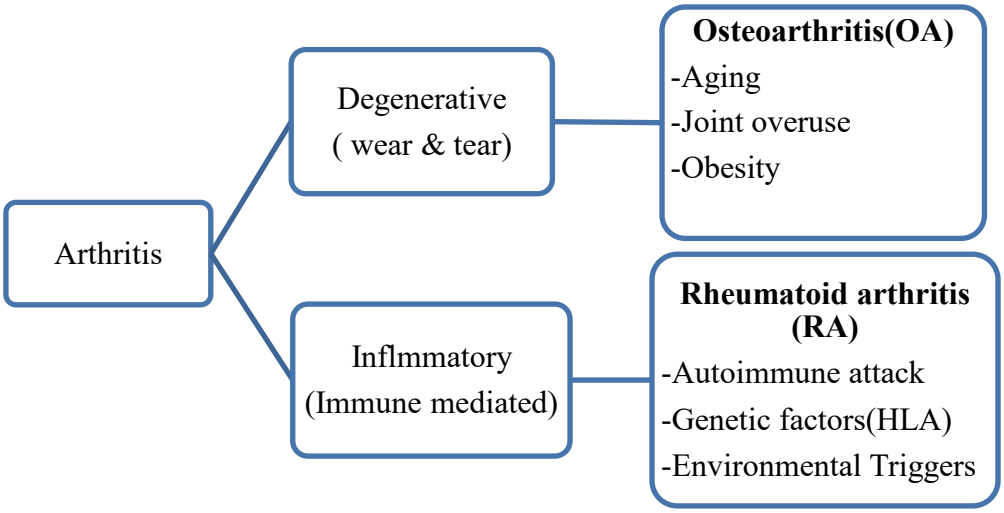


Figure 1: Diagrammatic representation of etiology of arthritis.

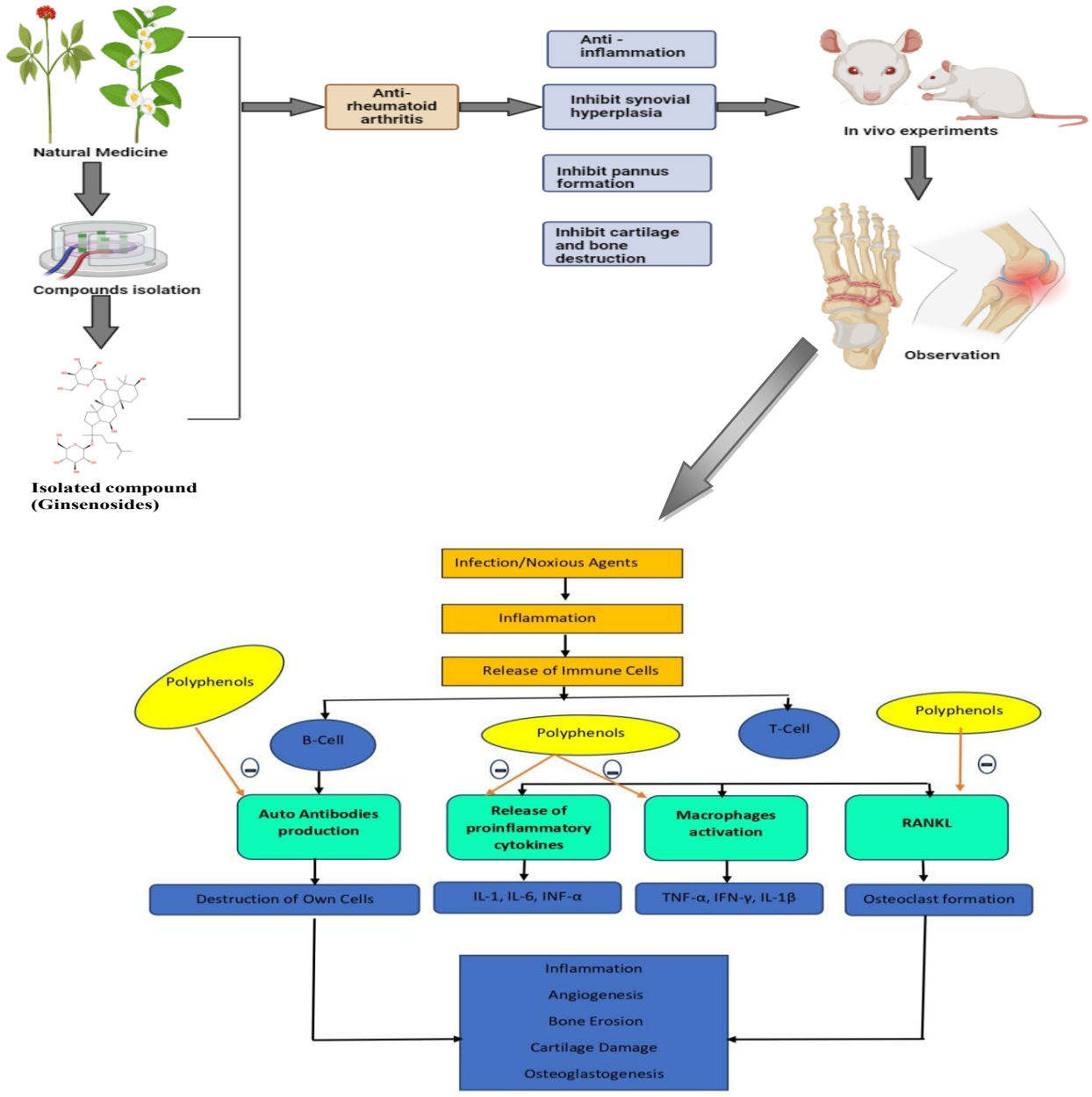


Figure 1: Overview of Inflammo-modulation by potent bioactives (Polyphenol) via T-cell and B-cells mediated signalling.

Demographic profile:

In this paper, we have tried to gather the age and prevalence basis data of rheumatoid arthritis (RA) and osteoarthritis (OA). Nowadays, Arthritis (RA and OA) has been a concerning disorder. We gather the data in India and worldwide based on surveys and reports. There are roughly 9.2 million people with RA in India, which represents 0.92% of the adult population. The disease primarily affects women, and it is more common in those between the ages of 20 and 40 [13]. About 18 million people worldwide suffer from RA, with women making up around 70% of that afflicted. In 2019, rheumatoid arthritis affected 18 million persons globally [14]. Women make up over 70% of those with rheumatoid arthritis, and 55% of those over 55 have the disease. Rehabilitation could be beneficial for 13 million individuals with moderate to severe rheumatoid arthritis [15].The data has been graphically represented below:

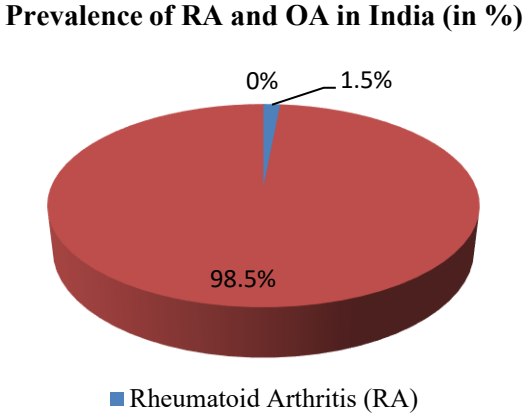


Figure 3: Graphical representation of prevalence of RA and OA in India.

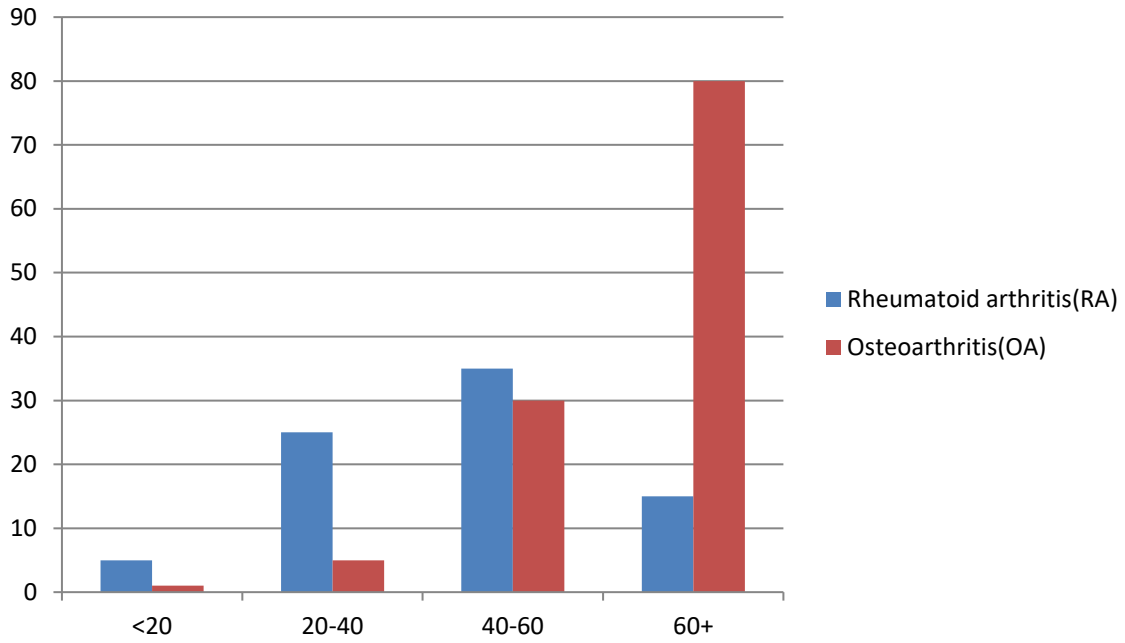


Figure 4: Graphical representation of prevalence of RA and OA by age group.

Table 1: Comparison between RA and OA.

Feature	Rheumatoid Arthritis (RA)	Osteoarthritis (OA)	Ref
Prevalence	0.92% in India, 1% globally	62.35 million in India, 595 million globally	16
Gender distribution	Predominantly women, 70% of global cases	Predominantly women, especially over 55	17
Age group affected	Mostly 20-40 years in India, older adults globally	Primarily older adults, more common post-55	18
Common joints affected	Hands, wrists, knees	Knees, hips, hands	
Risk factors	Genetics, smoking, autoimmune triggers	Age, obesity, joint injuries	
Impact	Significant disability, especially in younger adults	Disability due to joint degeneration in elderly	

2. Pathophysiology of arthritis:

The pathophysiology of arthritis varies depending on the type but generally involves a combination of inflammation, cartilage degradation, and bone remodeling. Pro-inflammatory cytokines including TNF-α, IL-1, and IL-6 are released when immune cells infiltrate the synovium due to an autoimmune reaction in inflammatory arthritis, such as rheumatoid arthritis [19]. This encourages angiogenesis, pannus development, and synovial hyperplasia, all of which weaken bone and cartilage [20].

2.1 Pathophysiology of Osteoarthritis: Osteoarthritis (OA) is a degenerative joint disease characterized by the progressive breakdown of articular cartilage, subchondral bone remodeling, synovial inflammation, and the formation of osteophytes (bone spurs) [21]. Mechanical stress and metabolic alterations that result in chondrocyte dysfunction are the first signs of the disease [22]. When these chondrocyte, which are in charge of preserving cartilage, become unbalanced, they produce too many matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), which degrade collagen and proteoglycans and cause cartilage erosion [23]. The underlying subchondral bone experiences sclerosis and cyst development as cartilage degrades, which exacerbates joint pain and stiffness [24]. The pro-inflammatory cytokines include IL-1β, TNF-α, and IL-6 causes synovial inflammation, which starts cartilage degradation and increases pain by activating nerve endings [25].

2.2 Pathophysiology of Rheumatoid arthritis (RA): Inflammation of the synovial joints causes joint damage and possible deformity in rheumatoid arthritis (RA), a chronic inflammatory disease [26]. Environmental variables, dysregulated immune responses, and genetic predisposition all contribute to the Pathophysiology of RA [27]. By altering immune system function, genetic risk factors specifically, changes in the HLA-DRB1 gene predispose people to RA [28]. In people who are genetically predisposed, environmental triggers like smoking and infections can cause the condition to start

by causing the synthesis of citrullinated proteins, which the immune system mistakenly interprets [29]. This sets off an autoimmune reaction in which the body's immune system produces rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), which result in the creation of immune complexes that accumulate in the synovium [30]. These complexes trigger the release of pro-inflammatory cytokines such TNF-α, IL-1, and IL-6 by activating T-cells, B-cells, and macrophages [31]. Chronic inflammation is fueled by the cytokines, which thicken and inflame the synovium, resulting in the formation of a proliferative tissue known as pannus [32]. Bone resorption and cartilage deterioration result from the pannus' invasion of the bone and cartilage. Additionally, the generation of matrix metalloproteinases, which degrade joint structures, is stimulated by activated immune cells [33]. Deformities, loss of function, and joint degradation are the outcomes. Systemic inflammation can also result in extra-articular symptoms such vasculitis, cardiovascular illness, and exhaustion [34]. Untreated or insufficiently managed RA can cause gradual joint deterioration and disability over time. The Pathophysiology of the disease is mostly based on the interaction of autoimmunity, inflammation, and tissue damage [35].

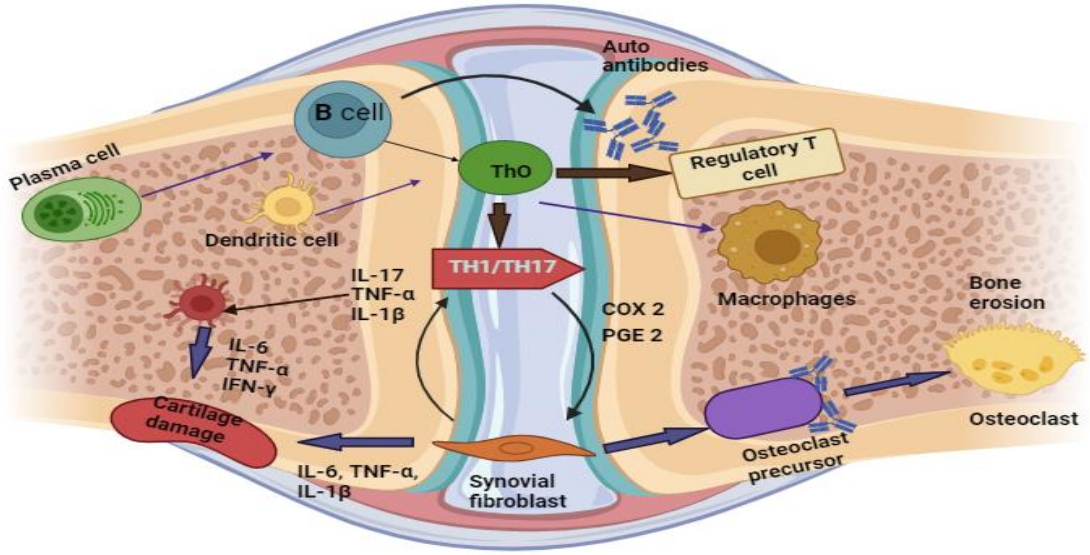


Figure 5: A diagrammatic representation of pathophysiology of Rheumatoid Arthritis (RA).

Table 2: Molecular Target in Rheumatoid Arthritis

S. No.	Molecular Targets	Role	Occurrence	Example of Targeting Drugs	Ref
1.	Cyclooxygenase pathway	Prostanoid biosynthesis, which produces biologically active compounds implicated in inflammation and other clinical problems	Cytosol and tissue	Celecoxib, Piroxicam, Naproxen, Valdecoxib	36
2.	Tumor Necrosis Factor-α	MMPs, adhesion molecules, endothelial cells, synovial fibroblasts, macrophages, and the release of additional cytokines and PGs are all activated.	Synovial fluid and tissue	Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab pegol	37
3.	Interleukin-1	Strong MMP and eicosanoid inducer, NF-κB ligand receptor activator, and hyaline cartilage formation inhibitor.	Synovium	Anakinra	38
4.	Interleukin-6	Intercellular cell adhesion molecules 1 expression is upregulated, bone resorption occurs, and osteoclast activation occurs.	Serum and synovial fluid	Tocilizumab, lactoferin	39
5.	Interleukin-8	Neutrophil Recruitment, Inflammatory Response, Angiogenesis, Cartilage and Bone Degradation	Synovium	ABX-IL8	40
6.	Interleukin-10	Reduce cytokine production and increase	Synovial	Pegilodecakin (AM0010),	41

		IL-1RA production along	tissue	AMG 108, MDX-1100	
7.	Matrix Metalloproteinase	Involved in the deterioration of bone and cartilage	Joint Synovium	Trocade (Ro 32-3555)	42
8.	Nuclear Factor-κB	Immune Response Regulation, Cell Survival and Apoptosis, Stress and Oxidative Response	Cytosol	Iguratimod	43
9.	Prostaglandin (PG)	Inducing bone resorption	Osteocyte	Celecoxib, Piroxicam, Naproxen, Valdecoxib	44
10.	B lymphocyte	Presentation of antigens and pro-inflammatory cytokine secretin	Bone marrow, synovial membrane	Rituximab	45

3. Conventional treatment options for Rheumatoid arthritis:

3.1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs): DMARDs are effective in treating inflammatory joint illnesses, including RA; medications lessen the immunological reactions that cause pain and inflammation and slow the progression of joint deterioration [46]. If an entity has demonstrated its ability to prevent or postpone joint deterioration in RA on hand or foot radiographs, it is deemed disease-modifying. There are two main categories of DMARDs: conventional and biological DMARDs [47]. Biologic DMARDs are soluble receptors or monoclonal antibodies, while conventional DMARDs include medications like methotrexate and sulfasalazine [48].

3.1.1 Conventional Synthetic DMARDs (csDMARDs): The conventional DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, cyclosporine, gold salts, D-penicillamine, and tetracycline [49]. It is traditional, non-biologic DMARDs that mainly suppress the immune system and have a slow half-life of several weeks. Methotrexate reduces the availability of folate ion, which is important for DNA synthesis and cellular growth, by inhibiting dihydrofolate reductase, also inhibits inflammatory immune cells that divide quickly and decreases the synthesis of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) [50]. Sulfasalazine inhibit the nuclear factor kappa-B (NF-kB), transcription factor, TNF-alpha expression by inducing caspase 8-induced apoptosis in macrophages, also inhibit the osteoclast development by inhibiting the expression of receptor activator of NF-kB ligand (RANKL) and osteoprotegerin; sulfasalazine inducethe conversion of adenine nucleotides to adenosine and its anti-inflammatory properties mediated by adenosine; inhibition of leukocyte accumulation through an adenosine-dependent mechanism; inhibition of B-cell function; and inhibition of the release of inflammatory chemokines interleukin-8, on the other side the Hydroxychloroquine interferes with antigen presentation and inhibits toll-like receptor signaling, reduce the activation of immune cells and decreasing cytokine production [51, 52, 53].

3.1.2 Biologic DMARDs includes monoclonal antibodies, fusion proteins, therapeutic proteins, and deoxyribonucleic acid vaccines. They have incredibly complicated structures and are often 200–1000 times larger than a small molecule medicine [54]. Significant progress has been made in the treatment of RA since the introduction of these biological DMARDs. Etanercept suppresses the pro-inflammatory cytokine effects. Because of its shape, it can bind TNF 50–1000 times more strongly than naturally occurring TNF receptors [55]. 50 mg or 25 mg is the subcutaneous dosage that is given once or twice a week respectively; the half-life is three to six days. Patients were examined using either methotrexate combination therapy or etanercept monotherapy, and combination therapy produced better outcomes than monotherapy [56]. Etanercept can frequently be maintained at half the usual dosage in RA patients who have reached a stable low disease activity state while taking methotrexate plus it [57]. Infliximab is a chimeric (mouse Fv1, human IgG1) monoclonal antibody that forms stable, non-dissociating immune complexes by binding directly to soluble TNFα and membrane-binding with high affinity [58]. Since infliximab is a bivalent monoclonal antibody that permits the formation of multimeric complexes, it binds two soluble TNF trimers at the same time. Additionally, it increases recurrent signals and binds firmly to human cell TNF membranes. The dosage is determined by the patient's body weight and is typically between 3 and 10 mg/kg. It has a half-life of 7.7 to 9.5 days. Methotrexate is used in combination with infliximab. It increases the TNF blocker's effectiveness [59].

3.2 Non-steroidal Anti-inflammatory Drugs (NSAIDs): NSAIDs mainly inhibit the cyclooxygenase (COX) enzymes, COX-1 and COX-2, which is responsible for prostaglandin synthesis [60]. Lipid substances called prostaglandins mediate heat, discomfort, and inflammation. While COX-2 is inducible and mostly engaged in inflammatory reactions, COX-1 is constitutively produced and contributes to renal function, platelet aggregation, and the integrity of the gastrointestinal mucosa [61]. NSAIDs decrease prostaglandin synthesis by inhibiting COX enzymes, which lowers inflammation, analgesia, and antipyresis

[62]. Another side, COX-1 inhibition may have negative consequences such as increased risk of bleeding, renal impairment, and stomach ulcers. In order to reduce gastrointestinal adverse effects while maintaining anti-inflammatory effectiveness [63].

3.3 Corticosteroids have strong anti-inflammatory and immunosuppressive effects; they are frequently used as part of the traditional treatment for RA [64]. It lessens discomfort, control inflammation, and shield joints from harm. Corticosteroids suppress the immune system by inhibiting the pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6) that play a key role in RA, also blocking the inflammatory pathways, reducing leukocyte activity and inhibiting the prostaglandins and leukotrienes; these molecules are involved in pain and inflammation; corticosteroids suppress the production of pro-inflammatory cytokines. Prednisone, methyl prednisolone, dexamethasone, hydrocortisone are the commonly used corticosteroids in RA [65].

4. Prominent Herbal Bioactives Targeting RTKs in Arthritis:

According to many surveys and reports, we found that herbal medications are frequently chosen over conventional therapies because of their natural nature, perceived safety, and all-encompassing approach to healing. Many people think that herbal treatments are a kinder option for long-term use because they have fewer side effects than synthetic pharmaceuticals. Furthermore, herbal remedies have long been a crucial component of traditional medicinal systems, providing cultural importance and a sense of confidence. They are also more readily available and less expensive than a lot of pharmaceutical medications, which makes them a desirable option for anyone looking for economical medical care. Furthermore, herbal medicines frequently promote a balanced and preventive approach to health by concentrating on general well-being rather than only treating particular symptoms.The potential of herbal bioactive substances to modify tyrosine kinase pathways for the treatment of arthritis, especially rheumatoid arthritis (RA), has been investigated in recent studies. Through a variety of mechanisms, several natural substances have shown that encouraging anti-inflammatory and anti-arthritic effects.

Table 3: Classification and characteristics of the human RTKs and Human non receptor tyrosine kinase

Class	Family Name	Members	Molecular characteristics of the extracellular domains
Human Receptor Tyrosine Kinase: [66-71]			
I	EGFR	EGFR, ERBB2, ERBB3, ERBB4	2 cysteine-rich domains
II	Insulin R	INSR IGFR	2 chains α and β, with one cysteine-rich and 2 FNIII domains
III	PDGFR	PDGFRα, PDGFRβ, M-CSFR, KIT, FLT3L	5 Ig-like domains
IV	VEGFR	VEGFR1, VEGFR2, VEGFR3	7 Ig-like domains
V	FGFR	FGFR1, FGFR2, FGFR3, FGFR4	3 Ig-like domains, 1 acidic box
VI	CCK	CCK4	7 Ig-like domains
VII	NGFR	TRKA, TRKB, TRKC	2 Ig-like domains, rich leucin domains
VIII	HGFR	MET, RON	1 transmenbrane a chain linked with one extracellular b chain
IX	EPHR	EPHA1 to6, EPHB1to 6	1 Ig-like, 1 cysteine-rich and 2 FNIII-like domains
X	AXL	AXL, MER, TYRO3	2 Ig-line, 2 FNIII-like domains
XI	TIE	TIE,TEK	2 Ig-like, 1 EGF, and 3 FNIII-like domains
XII	RYK	RYK	1 transmenbrane b chain linked with one extracellular a chain
XIII	DDR	DDR1, DDR2	1 discoidin-like domain
XIV	RET	RET	1 cadherin-like domain
XV	ROS	ROS	6 FNIII-like domains
XVI	LTK	LTK, ALK	1 cysteine-rich domain
XVII	ROR	ROR1, ROR2	1 Ig-domain, 1 cysteine-rich domain and one kringle-like domains

XVIII	MUSK	MUSK	4 Ig-like and 1 cysteine-rich domains
XIX	LMR	AATYK1, AATYK2, AATYK3	A short extracellular domain
XX	Undetermined	RTK106	A short receptor chain with a short extracellular domain
Human non receptor tyrosine kinases:[72-76]			
I	ABL	ABL1, ABL2 (ARG)	Tyrosine Kinase Domain
II	ACK	TNK1, TNK2 (ACK1)	CRIB (Cdc42/Rac Interactive Binding) Domain
III	CSK	CSK, MATK	SH3 (Src Homology 3) Domain
IV	FAK	PTK2 (FAK). PTK2B (PYK2)	Proline-rich Domains (PRR)
V	FES	FER, FES	F-BAR (FES-CIP4 Homology-Bin-Amphiphysin-Rvs) Domain
VI	FRK	FRK, PTK6 (BRK), SRMS	SH3 (Src Homology 3) Domain, SH2 (Src Homology 2) Domain
VII	JAK	JAK1, JAK2, JAK3,TYK2	Pseudo-Kinase (JH2) Domain
VIII	SRC-A	FGR, FYN, SRC, YES1	SH4 (Src Homology 4) Domain
IX	SRC-B	BLK, HCK, LCK, LYN	Tyrosine Kinase (Catalytic) Domain
X	TEC	BTK, ITK, TEC, TXK	PH (Pleckstrin Homology) Domain, TH (Tec Homology) Domain
XI	SYK	SYK, ZAP70	N-terminal Tandem SH2 (Src Homology 2) Domains

4.1 Herbal bioactives for Rheumatoid Arthritis (RA): After thousands of years of development and accumulation of clinical experience, herbal medicine has formed a unique theoretical system. Herbal bioactives usually contain a variety of active ingredients, providing an excellent source for the discovery of anti-inflammatory and analgesic drugs. The molecular structures of these compounds are illustrated in Fig. 6.

4.1.1 Curcumin (*Curcuma longa***):** *Curcuma longa* (Mol. Formula: $C_{21}H_{20}O_6$ and a molecular weight: 368.38 g/mol.) contains curcumin, a naturally occurring polyphenol molecule with potent anti-inflammatory and antioxidant properties [77]. According to modern pharmacology, curcumin is a beneficial active ingredient for the prevention and treatment of arthritis. It has been demonstrated that curcumin inhibits the activity of a number of tyrosine kinases, including JAK1/2 and Src. Pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β are produced as a result of intracellular signaling cascades that are started by Src and JAK kinases and contribute to the pathophysiology of RA [78]. Curcumin, the active component of turmeric, has been studied for its interaction with receptor tyrosine kinases (RTKs) in arthritis, particularly in rheumatoid arthritis (RA) and osteoarthritis (OA). Curcumin modulate RTKs, affecting pathways involved in inflammation, immune responses, and cartilage homeostasis. Curcumin inhibits VEGFR-2, reducing angiogenesis and inflammation in synovial tissue, which is a hallmark of rheumatoid arthritis [79]. EGFR signaling is involved in synovial fibroblast proliferation, which contributes to joint damage in RA. Curcumin down regulates EGFR phosphorylation, leading to reduced fibroblast activity and synovial hyperplasia. PDGFR (Platelet-Derived Growth Factor Receptor) is involved in fibrosis and joint tissue re-modelling. Curcumin interferes with PDGFR-mediated pathways, preventing fibrosis and joint destruction. FGFR (Fibroblast Growth Factor Receptor) signaling contributes to cartilage degradation in OA [80]. Curcumin inhibits FGFR activation, reducing cartilage breakdown and promoting chondroprotection. Insulin-like Growth Factor Receptor (IGF-1R) is important for chondrocyte survival and joint repair. Curcumin may help balance IGF-1R signaling, promoting cartilage repair while reducing inflammation [81]. Apart from these, Curcumin blocks downstream signaling of RTKs, such as MAPK, PI3K/Akt, and NF-κB, leading to reduced inflammation. From these, it has been observed and concluded that, Curcumin may slow cartilage degradation and promote repair, suppresses aggressive synovial fibroblast proliferation, reducing pannus formation in RA. While preclinical studies support its benefits, further clinical trials are needed to establish its effectiveness as a targeted RTK inhibitor in arthritis therapy [82].

4.1.2 Berberine: Plants including *Coptis chinensis* (goldenseal) and *Berberis vulgaris* (barberry) contain Berberine (Mol. Formula: $C_{20}H_{18}NO_4$ and molecular weight: 336.367 g/mol.), naturally occurring alkaloid that has drawn interest as a possible immunomodulatory and anti-inflammatory treatment for RA. The signal transduction of cytokines such as IL-6, IL-1, and TNF-α depends on JAK2, which is a part of the JAK-STAT pathway. It also lowers the activity of downstream signaling proteins including STAT3, which is important in the transcription of genes linked to inflammation and immunological responses in RA, by blocking JAK2 and Src [83]. Berberine affects the immune system and indirectly lowers the inflammatory responses by activating AMPK. Additionally, its activation controls NF-κB, which reduces inflammation in RA.A naturally occurring isoquinoline alkaloid (Berberine) has demonstrated potential in regulating

receptor tyrosine kinases (RTKs) implicated in the pathophysiology of rheumatoid arthritis (RA) [84]. By blocking important RTKs including vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR), it suppresses pathological angiogenesis and synovial hyperplasia, two factors that lead to joint inflammation and injury. Berberine also inhibits RTK-mediated signalling pathways, such as PI3K/Akt and MAPK, which lowers the production of inflammatory cytokines and the proliferation of fibroblast-like synoviocytes [85]. Additionally, it alters insulin-like growth factor 1 receptor (IGF-1R) signalling, which encourages hyper proliferative synoviocytes to undergo apoptosis and stops the thickening of the synovium. These effects demonstrate berberine's anti-inflammatory, anti-angiogenic, and anti-proliferative properties, which make it a viable option for treating RA via modulating RTK [86].

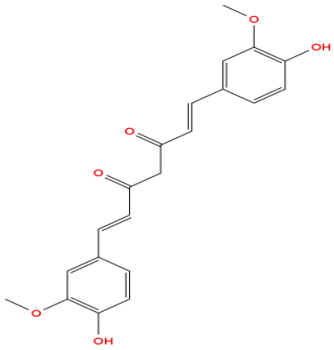
4.1.3 Ginseng (Ginsenosides): Ginseng (Panax ginseng, Panax quinquefolius) is a well-known medicinal herb with potent anti-inflammatory, immunomodulatory, and antioxidant properties [87]. A recent study shows that it can block tyrosine kinase, which may help to treat rheumatoid arthritis (RA).Tyrosine kinases (TKs) are crucial in immune signaling, inflammation, and synovial fibroblast activation in RA. It is a well-liked herbal treatment that helps the body deal with stress because of its adaptogenic qualities. The active ingredients in ginseng, called ginsenosides (Mol. formula: $C_{42}H_{72}O_{14}$ and a molecular weight: 801.01 g/mol.), block the signalling pathways for MAPK (mitogen-activated protein kinase) and JAK/STAT [88]. Ginseng, a well-known herbal medicine rich in ginsenosides, has demonstrated potential in modulating receptor tyrosine kinases (RTKs) involved in rheumatoid arthritis (RA). It has been demonstrated that several ginsenosides, including Rg1 and Rb1, interact with RTKs such as vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR), suppressing angiogenesis and synovial hyperplasia, two important pathogenic characteristics of RA. Furthermore, ginseng suppresses downstream signalling pathways controlled by RTK, such as PI3K/Akt and MAPK, which lowers the production of inflammatory cytokines and fibroblast-like synoviocyte proliferation [89]. Ginseng prevents excessive synovial thickening by promoting apoptosis in hyper proliferative synoviocytes through modulation of the insulin-like growth factor 1 receptor (IGF-1R).Additionally, ginseng can indirectly control the JAK/STAT pathway through RTK, which lowers levels of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. These combined results imply that ginseng may have anti-inflammatory, anti-angiogenic, and anti-proliferative properties through RTK regulation, making it a promising natural treatment agent for RA [90].

4.1.4 EpigallocatechinGallate (EGCG): The main catechin in green tea (Camellia sinensis), epigallocatechin gallate (Mol. formula: it $C_{22}H_{18}O_{11}$ and a molecular weight: 458.37 g/mol.), has shown potent anti-inflammatory, immunomodulatory, and antioxidant qualities. Tyrosine kinase inhibition partially mediates its actions in RA, making a promising natural chemical for RA treatment. Epigallocatechin-3-gallate (EGCG) inhibited the production of osteoclasts by preventing the activation of RANKL, which in turn prevented the development of osteoblasts [91]. The expression of nuclear factor-activated T cells c1, a transcription factor necessary for osteoclast development, is down regulated by RANKL of the JNK and NF-kB pathways. Patients suffering from RHA are unable to stop synovial fibroblasts from dying. Treatment with EGCG has been shown to increase sensitivity to synovial fibroblast apoptosis by suppressing the expression of myeloid cell leukemia -1 [92]. The main catechin in green tea, epigallocatechin gallate (EGCG), has been demonstrated to interact with receptor tyrosine kinases (RTKs) implicated in the pathophysiology of rheumatoid arthritis (RA). By blocking important RTKs including vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR), EGCG reduces synovial hyperplasia and pathological angiogenesis, two processes that lead to joint inflammation and degeneration [93]. Furthermore, EGCG inhibits RTK-mediated signalling pathways, including as PI3K/Akt and MAPK, which results in decreased fibroblast-like synoviocyte proliferation and pro-inflammatory cytokine production. Additionally, by modifying the insulin-like growth factor 1 receptor (IGF-1R), it encourages hyperactive synoviocytes to undergo apoptosis and inhibits excessive synovial thickening [94]. EGCG further reduces inflammatory mediators like TNF-α, IL-6, and IL-1β by indirectly influencing the JAK/STAT pathway through RTK crosstalk. Because of these combined actions, EGCG is a viable natural therapy candidate for RA through RTK regulation, highlighting its potential as an anti-inflammatory, anti-angiogenic, and anti-proliferative drug [95].

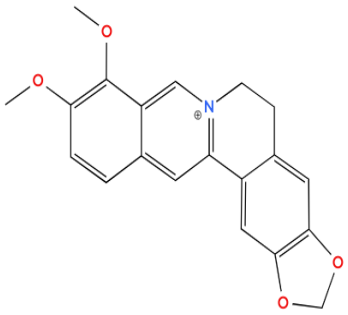
4.1.5 Withaferin A: The bioactive compound derived from *Withania somnifera* (Ashwagandha), exhibits potent anti-inflammatory and immunomodulatory effects, making it a promising bioactive for managing rheumatoid arthritis (RA) through tyrosine kinase inhibition [96]. Tyrosine kinase inhibition makes Withaferin A (Mol. formula: $C_{28}H_{38}O_6$ and molecular weight: 470.606 g/mol.), a bioactive molecule extracted from *Withania somnifera* (ashwagandha), a prospective treatment option for rheumatoid arthritis (RA), due to its strong anti-inflammatory and immunomodulatory properties. Tyrosine kinases such spleen tyrosine kinase (Syk), Janus kinase (JAK), and Src family kinases are essential for immune cell activation, cytokine generation, and synovial fibroblast proliferation in the pathophysiology of RA [97]. RTKs play a crucial role in the pathogenesis of RA by mediating signaling pathways that drive inflammation, synovial hyperplasia, and joint destruction.By blocking RTK phosphorylation and downstream signalling cascades, including the PI3K/Akt and MAPK pathways, withaferin A inhibits the generation of pro-inflammatory cytokines and the proliferation of fibroblast-like synoviocytes [98]. Withaferin A also has anti-angiogenic qualities, which help to lessen pannus development and synovial inflammation in RA. Its potential as a natural medicinal

drug for modifying RTK-mediated degenerative processes in rheumatoid arthritis is highlighted by these pathways [99].

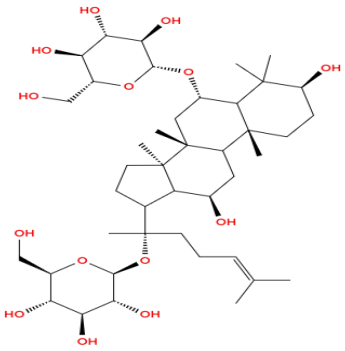
4.1.6 Boswellic acids: Boswellic acids (mol. formula: $C_{30}H_{48}O_3$ and a molecular weight: 456.7 g/mol.) are the active compounds found in Boswellia serrata (also known as Indian frankincense). These are known for anti-inflammatory, pain-relieving, and immune-modulating properties, making them essential for managing conditions like arthritis and inflammatory diseases [100].The production of pro-inflammatory cytokines in RA is dependent on JAK-STAT signaling, which is inhibited by Boswellic acids. They lessen the activation of important inflammatory mediators by inhibiting this route. Additionally, it inhibits 5-lipoxygenase, an enzyme that catalyses the synthesis of leukotrienes, inflammatory mediators that exacerbate joint discomfort and damage in RA. Boswellic acids decrease the release of cytokines including TNF-α, IL-6, and IL-1β by inhibiting JAK-STAT and 5-LOX, which helps to lessen pain and inflammation [101]. RTKs including the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR) are involved in angiogenesis, joint degeneration, and synovial inflammation in RA. By altering phosphorylation events, boswellic acid suppresses RTK signalling and lowers the activation of downstream pathways like PI3K/Akt and MAPK, which are implicated in synovial proliferation and inflammatory responses [102]. Boswellic acid reduces joint inflammation and stops the progression of RA by targeting RTKs and having anti-inflammatory and anti-proliferative actions. By interfering with important signalling cascades that cause inflammation and tissue damage, boswellic acid has the potential to be used as a natural medicinal drug to manage RA [103].



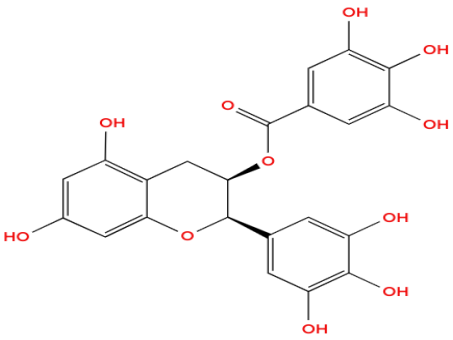
a.) Curcumin



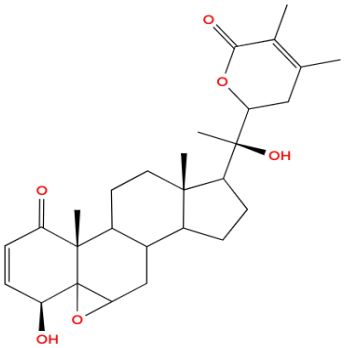
b.) Berberine



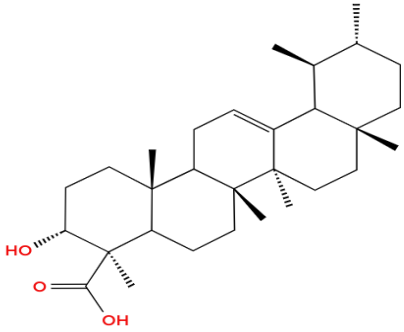
c.) Ginsenosides



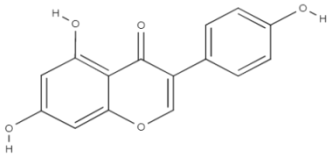
d.) Epigallocatechin Gallate



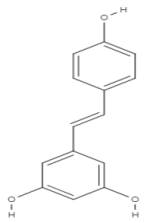
e.) Withaferin A



f.) Boswellic acids



g.) Genistein



h.) Resveratrol

Figure 6: Chemical structure of tyrosine kinase mediated herbal bioactive with anti-arthritic effect (fig. a; Curcumin, b; Berberine, c; Ginsenosides, d; Epigallocatechin Gallate, e; Withaferin A, f; Boswellic acid is used for RA and fig. g; Genistein, h; Resveratrol is used for OA).

4.2 Herbal bioactive for Osteoarthritis (OA): Tyrosine kinase pathways may be inhibited by herbal bioactives, offering an alternative to conventional OA therapies. Herbal bioactive substances that target tyrosine kinase pathways have demonstrated potential in the treatment of osteoarthritis (OA). These substances mainly work by altering signalling pathways linked to inflammation and cartilage deterioration. Here are the number of herbal bioactives and their possible function in TK targeting for OA treatment.

4.2.1 Genistein: Genistein (Mol. formula: $C_{15}H_{10}O_5$and a molecular weight: 270.240 $g \cdot mol^{-1}$), a soy-derived isoflavone, exhibits potent anti-inflammatory, chondroprotective, and antioxidant effects, making it a promising therapeutic agent for osteoarthritis (OA) [104]. Genistein exerts its protective effects through the inhibition of Epidermal Growth Factor Receptor (EGFR) and Src Tyrosine Kinase also it suppresses the Focal Adhesion Kinase (FAK) and PI3K/Akt Pathway [105]. Additionally, it inhibits topoisomerase II, which damages DNA and causes cancer cells to undergo apoptosis. It alters a number of signalling pathways that are implicated in inflammation, apoptosis, and cell cycle control, such as PI3K/Akt and NF-κB. Because of these various effects, genistein has been researched for possible advantages in osteoporosis, cardiovascular health, cancer prevention, and neuroprotection [106]. By blocking important RTKs such as vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR), it lowers pathological angiogenesis and synovial hyperplasia, two factors that lead to joint inflammation and injury. Furthermore, genistein suppresses the synthesis of pro-inflammatory cytokines and reduces the proliferation of fibroblast-like synoviocytes by down regulating RTK-mediated signalling pathways, such as PI3K/Akt and MAPK [107]. Additionally, it inhibits the insulin-like growth factor 1 receptor (IGF-1R), which encourages hyper proliferative synoviocytes to undergo apoptosis and stops excessive synovial thickening. Additionally, genistein indirectly affects the JAK/STAT pathway through RTK crosstalk, which lowers levels of inflammatory mediators like TNF-α, IL-6, and IL-1β [108]. Because of these combined actions, genistein is a viable natural therapy candidate for RA through RTK regulation, highlighting its potential as an anti-inflammatory, anti-angiogenic, and anti-proliferative drug [109].

4.2.2 Resveratrol: Resveratrol (Mol. formula: $C_{14}H_{12}O_3$ and a molecular weight of approximately 228.24 g/mol.), a polyphenol compound found in grapes, berries, and red wine, exhibits potent chondroprotective and anti-inflammatory properties in osteoarthritis (OA) by modulating tyrosine kinase signaling pathways [110].Resveratrol prevents cartilage degradation and preserves the extracellular matrix by inhibiting EGFR phosphorylation, which in turn lowers the expression of matrix metalloproteinases (MMP-1, MMP-3, and MMP-13).RTKs are essential for cell signalling pathways that control immunological responses, inflammation, and RA-related synovial hyperplasia [111]. Resveratrol works therapeutically by preventing RTK activation, which in turn down regulates downstream signalling cascades such the PI3K/Akt and MAPK pathways, which are in charge of synovial fibroblast proliferation and the production of inflammatory cytokines. Resveratrol efficiently lowers bone erosion, cartilage deterioration, and joint inflammation in RA by modifying these pathways [112]. Its anti-inflammatory and antioxidant qualities also aid in reducing oxidative stress and immunological dysregulation linked to the illness. Therefore, resveratrol's interaction with RTKs offers a viable path for the creation of new RA therapies that focus on the main molecular processes that underlie the course of the illness [113].

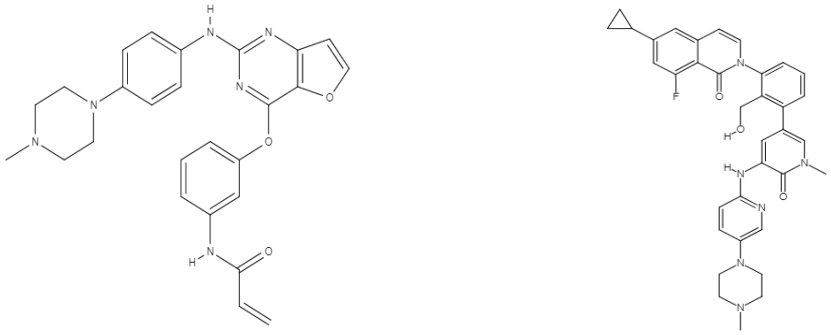
5. Drugs currently investigated in clinical trials:

We are gathering the data as of February 2025; clinical trials specifically investigating receptor tyrosine kinase (RTK)-mediated herbal bioactives for arthritis treatment are limited. There are the numbers of artificial small-molecule inhibitors that target RTKs specifically, Bruton's tyrosine kinase (BTK) are being studied in clinical settings for RA.

5.1 Poseltinib: An investigational Bruton's tyrosine kinase inhibitor called poseltinib (HM71224, LY3337641) is used to treat rheumatoid arthritis. The Hanmi Pharmaceutical has created it and Eli Lilly was granted a license to use it.In August 2016, rheumatoid arthritis patients started participating in phase II clinical studies [114]. There are some plans to conduct more phase II trials to treat immunological disorders such as Sjogren's disease, lupus, and lupus nephritis. Poseltinib is inhibiting the BTK, an essential enzyme in the B-cell receptor (BCR) signalling pathway. BTK is in

charge of myeloid and B cell activation, which results in the production of inflammatory cytokines, it also helps to lower the inflammation and immune system over activity in conditions like RA by inhibiting BTK [115]. Poseltinib has not yet received approval for clinical usage and is still undergoing clinical research.

5.2 RN486: RN486 is a potent and selective BTK inhibitor identified through structure-based drug design [116]. In rat models of inflammatory arthritis, preclinical research has shown dose-dependent efficacy and the potential to reduce B cell and myeloid cell-mediated aspects of the disease. A powerful and selective Bruton's tyrosine kinase (BTK) inhibitor, RN486 was created to treat autoimmune illnesses such as rheumatoid arthritis (RA). In B-cell receptor (BCR) signalling, BTK is an essential enzyme that plays a vital role in B-cell activation and cytokine release [117]. In order to reduce inflammation and immunological over activation without completely inhibiting the immune system, RN486 was created to specifically inhibit BTK. In rat models of inflammatory arthritis, preclinical research has shown that RN486 is effective in reducing tissue damage and joint inflammation in a dose-dependent manner [118].



a. Poseltinib b. RN486

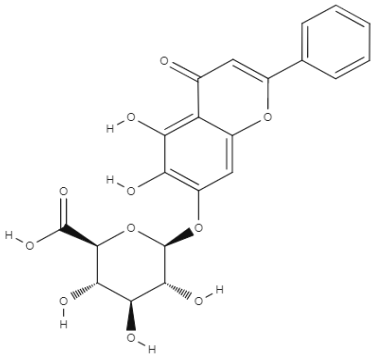
Figure 7: Chemical structures of drugs currently investigated under clinical trials.

6. List of Chinese herbs targeted to RTKs:

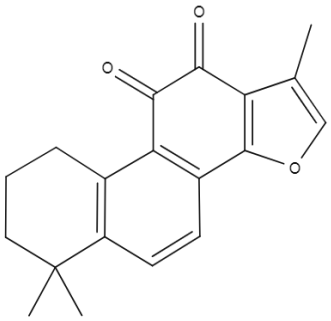
Receptor Tyrosine Kinase (RTKs) is significant targets in arthritis because of their involvement in inflammation, synovial growth, and angiogenesis [119]. There are various Chinese herbs and their bioactive components have been investigated for the effects on modulating RTKs (including VEGFR, EGFR, PDGFR, and FGFR) in arthritis-related disorders such as rheumatoid arthritis (RA) and osteoarthritis (OA). Here are the different types of Chinese herbs that have recognized or possible activity in targeting RTK:

Table 4: Chinese Herbs and Compounds Targeting RTKs in Arthritis

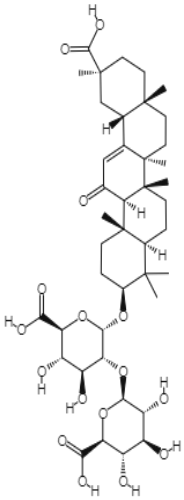
Herb	Active Compound(s)	Target RTK(s)	Mechanism / Effect
Scutellaria baicalensis (Huang Qin)	Baicalin, Baicalein	EGFR, VEGFR	Anti-inflammatory and anti-angiogenic; decreases downstream pathways and RTK phosphorylation
Salvia miltiorrhiza (Dan Shen)	Tanshinone IIA	VEGFR, PDGFR	By blocking RTKs and the PI3K/Akt pathway, it inhibits angiogenesis and synovial hyperplasia.
Glycyrrhiza uralensis (Gan Cao)	Glycyrrhizin, Licochalcone A	EGFR, FGFR	Anti-inflammatory; indirectly modifies RTK signalling
Tripterygium wilfordii (Lei Gong Teng)	Triptolide	EGFR, PDGFR	Potent immunosuppressive and anti-inflammatory properties; blocks RTK-mediated pathways
Epimedium spp. (Yin Yang Huo)	Icariin	VEGFR, PDGFR	Anti-osteoclastic, inhibits RTK to decrease inflammation and angiogenesis
Paeonia lactiflora (Bai Shao)	Paeoniflorin	VEGFR	Prevents the generation of inflammatory cytokines and synovial angiogenesis
Corydalis yanhusuo (Yan Hu Suo)	Tetrahydropalmatine	EGFR	Uses the RTK and MAPK pathways to alter pain and inflammation.
Ligusticum chuanxiong (Chuan Xiong)	Ligustilide, Ferulic acid	VEGFR	Prevents the growth of endothelial cells and neovascularisation



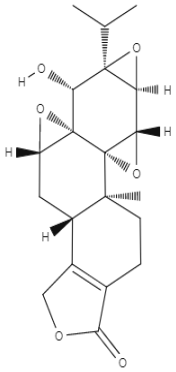
a. Baicalin



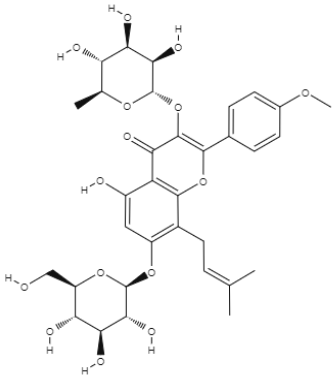
b. Tanshinone IIA



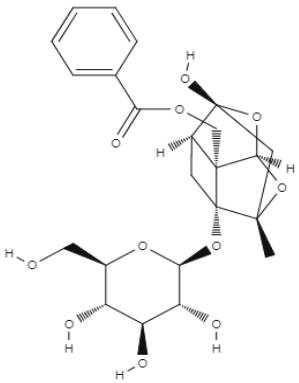
c. Glycyrrhizin



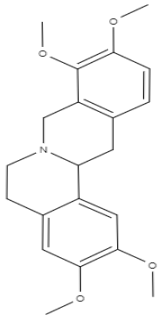
d. Triptolide



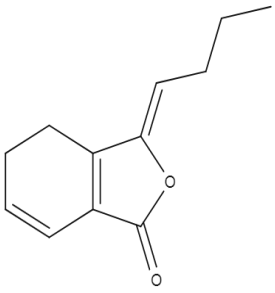
e. Icariin



f. Paeoniflorin



g. Tetrahydropalmatine



h. Ligustilide

Figure 8: Chemical structures of Chinese herbs targeted to RTKs.

Scutellaria baicalensis has baicalin and baicalein rich compound, lowers the activity of EGFR and VEGFR, resulting in diminished synovial inflammation and blood vessel growth [120]. *Salvia miltiorrhiza* has tanshinone IIA, which focuses on VEGFR and PDGFR to prevent neovascularization and the growth of synovial fibroblasts by disrupting the PI3K/Akt pathway[121]. *Glycyrrhiza uralensis*, containing glycyrrhizin and licochalcone A, indirectly influences RTK pathways like EGFR and FGFR, aiding its anti-inflammatory and tissue-protective properties[122].

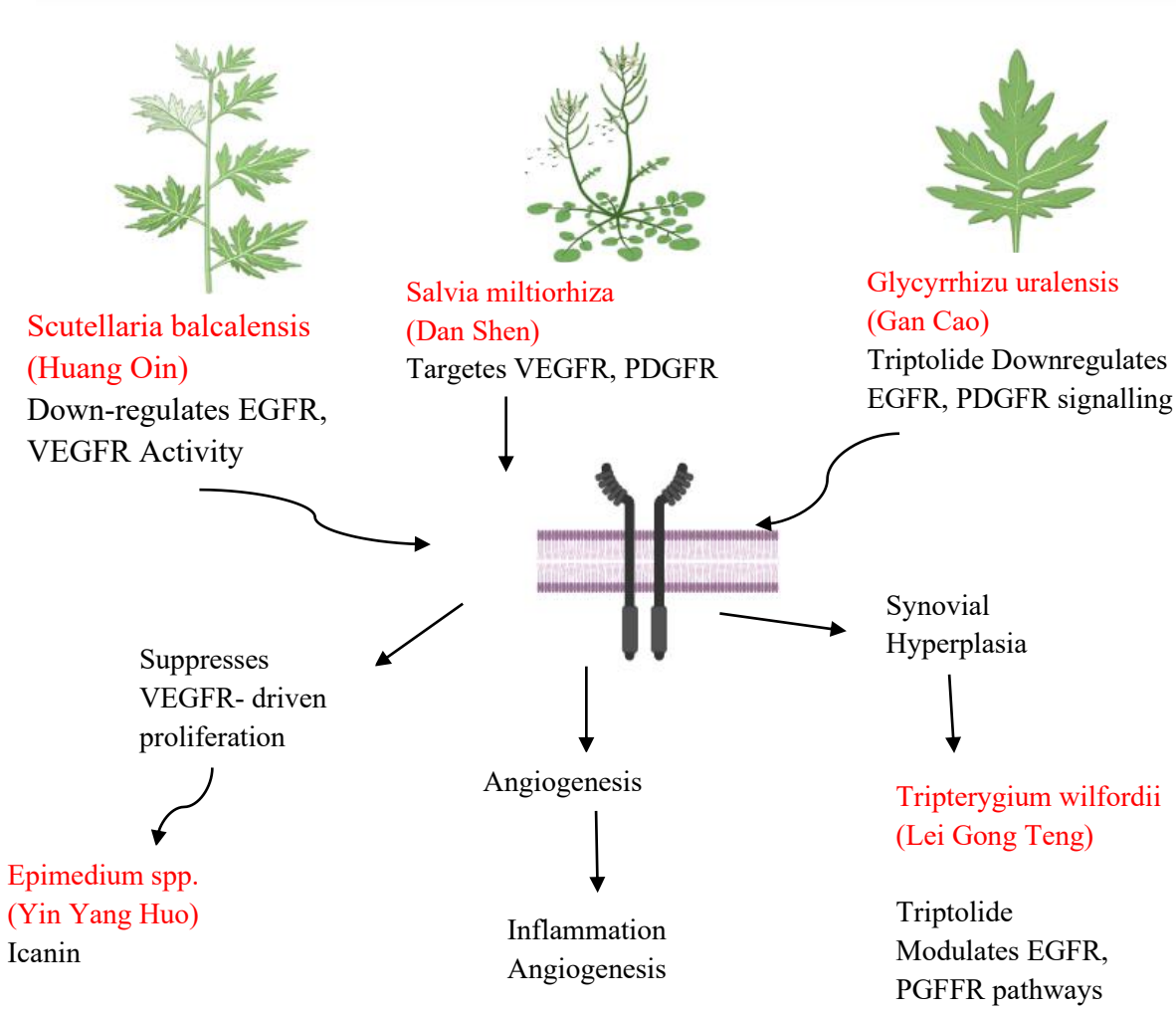


Figure 9: Chinese herbs and their bioactives targeted to RTKs

Tripterygium wilfordii, via triptolide, demonstrates strong immunosuppressive effects by inhibiting EGFR and PDGFR-related signaling, reducing inflammation and joint damage. [123] *Epimedium* species, especially because of icariin, reduce VEGFR and PDGFR activity, thereby restricting osteoclast development, blood vessel formation, and cartilage breakdown[124]. *Paeonia lactiflora* functions via paeoniflorin to decrease VEGFR-driven angiogenesis and cytokine production in synovial tissue[125]. *Corydalis yanhusuo*, containing tetrahydropalmatine, influences EGFR-related pathways, providing anti-inflammatory and pain-relieving advantages[126]. *Ligusticum chuanxiong*, which contains ligustilide and ferulic acid, inhibits VEGFR-induced endothelial growth, aiding in the decrease of synovial neovascularization and joint inflammation[127]. Collectively, these herbs offer a multi-faceted strategy for arthritis treatment through the modulation of RTK signaling pathways.

7. Challenges and Future Perspectives:

In recent years, the new insights on pathogenesis of arthritis has found, including the evidence of a persistent state of autoimmune disorder arthritis in affected joints, opened novel possible fields of research. This, together with recent data from herbal bioactives combination trials and biological drugs, led to new possibilities in potential therapeutic approach to RA and OA. The use of receptor tyrosine kinase (RTK)-mediated herbal bioactives for arthritis treatment presents both significant potential and notable challenges. One of the primary challenges in using herbal bioactives for receptor tyrosine kinase (RTK)-mediated arthritis treatment is their poor bioavailability and pharmacokinetics, as many herbal compounds, including resveratrol and withaferin A, suffer from rapid metabolism and limited systemic absorption, reducing their therapeutic efficacy. Additionally, the lack of

standardization and quality control in herbal formulations poses a challenge, as variations in extraction methods and plant sources lead to inconsistencies in bioactive concentrations. Furthermore, as most research is limited to preclinical models with few human trials, these bioactives are not commonly recognized as standard arthritis treatments due to a lack of clinical proof and regulatory obstacles, rather than using single-targeted therapy, combination methods are required due to the intricate pathophysiology of arthritis, which involves several inflammatory and oxidative stress pathways. Developing cutting-edge drug delivery methods like liposomal formulations and nanoparticles to improve bioavailability, combining herbal bioactives with traditional arthritis treatments for synergistic effects, and applying precision medicine techniques to customize therapies based on patient-specific biomarkers are some future perspectives. To prove the safety, effectiveness, and standardized dosage of these herbal treatments, more clinical studies and regulatory clearances are also necessary.

8. Conclusion and future perspective:

Herbal bioactives have emerged as prospective therapeutic agents for the treatment of autoimmune arthritis, with anti-inflammatory, immunomodulatory, and chondroprotective properties. Curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and boswellic acids have shown efficacy in preclinical and clinical research by targeting major inflammatory pathways like NF-κB, JAK/STAT, and MAPK signaling. These bioactives not only reduce symptoms, but they also assist modulate immune responses, slowing disease development and preventing joint damage. Despite their potential, problems still exist, including as bioavailability issues, herbal formulation uniformity, and long-term safety assessments. Future research should focus on optimizing delivery methods, which include Nanotechnology-based formulations, such as liposomes, nanoparticles, and micelles, can improve the solubility, stability, and absorption of bioactives like curcumin and resveratrol, hence increasing their therapeutic potential. Current research on synergistic herbal formulations suggests that combination therapy involving different bioactives with complimentary processes may provide increased efficacy while reducing the need for large doses, potentially reducing negative effects. With advances in pharmacogenomics and metabolomics, herbal bioactive treatments can be adjusted to specific genetic and metabolic profiles, resulting in more effective and targeted medicines for autoimmune arthritis patients. Herbal bioactives can be studied as adjunct therapy to traditional treatments such as DMARDs and biologics, with the potential to reduce drug resistance and side effects while enhancing patient outcomes.

List of Abbreviations:

ABL: Alveolar Bone Loss
ACK: Acetate Kinase
ACPAs: Anti-citrullinated protein antibodies
CCK: cholecystokinin
COX: Cyclooxygenase
CRIB: Cdc42/Rac Interactive Binding
CSK: C-terminal Src kinase
DMARDs: Disease-modifying anti-rheumatic medications
EGCG: Epigallocatechin gallate
EGFR: Epidermal Growth Factor Receptor
FAK: Focal adhesion kinase
F-BAR: FES-CIP4 Homology-Bin-Amphiphysin-Rvs
FES: Functional electrical stimulation
FGFR: Fibroblast growth factor receptor
FRK: Fyn-related kinase
HGFR: Hepatocyte growth factor receptor
IL-1: Interleukin-1
JAK: Janus-kinase
JH2: Pseudo-Kinase
JIA: Juvenile Idiopathic Arthritis
LMR: Lymphocyte-to-Monocyte Ratio
LTK: Leukocyte tyrosine kinase
MMPs: Matrix metalloproteinases
MUSK: Moschus moschiferus
NFκB: NuclearFactor-κB
NGFR: Nerve Growth Factor Receptor
NSAIDs: Non-steroidal anti-inflammatory drugs
OA: Osteoarthritis
PDGFR: Platelet-derived growth factor receptor
PG: Prostaglandin
PH: Pleckstrin Homology
PRR: Proline-rich Domains
RA: Rheumatoid Arthritis
RET: Relative enhancement
RF: Rheumatoid factor
ROR: Retinoic Acid Receptor-Related Orphan Receptor
ROS: Reactive oxygen species
RTKs: Receptor Tyrosine Kinase
SH2: Src Homology 2
SH3: Src Homology 3
SH4: Src Homology 4
SYK: Spleen tyrosine kinase
TEC: Tectorigenin
TH: Tec Homology
TNF: Tumor necrosis factor
TNF-α: Tumor necrosis factor- alpha
VEGFR: Vascular endothelial growth factor receptor
WHO: World Health Organization

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Author's Contributions:

Trilochan Satapathy: Review and Proof reading.

Nikita Patel: Conceptualization, Writing – original draft preparation

Poonam Sahu: Review and Proof reading

Pratibha Dhiwar: Visualization

Kamaksha Tiwari: Grammar Correction

Laxmi Sahu: Tables and Figures

References:

1. Li Z. Auto-Immune Diseases Caused by Overactive Immune System. Topics in Health and Biomedical Engineering. 2018;1(1):6-8. https://doi.org/10.26480/wcmpr.01.2018.06.08
2. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain. 1995 Dec 1;63(3):289-302. https://doi.org/10.1016/0304-3959(95)00186-7
3. Ali S, Ali SA, Kondrapu P, Tripathi N, Kumar PB, Prasad PD, Tonape MM, Terse PP, Ameen MP M, Kumar S, Saha A. A brief review of pathophysiology and management of different types of arthritis.
4. Hasan AA, Khudhur HR, Hameed AK. Rheumatic autoimmune diseases (focus on RA): prevalence, types, causes and diagnosis. Karbala Journal of Pharmaceutical Sciences. 2022 Jan 1;1(20).
5. Costa DS. Prevalence, burden and healthcare needs of people living with Osteoarthritis in Portugal: contribution to the development of a Model of Care (Doctoral dissertation, Universidade NOVA de Lisboa (Portugal)).
6. Mrid RB, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. Biomedicine & Pharmacotherapy. 2022 Jul 1;151:113126. https://doi.org/10.1016/j.biopha.2022.113126
7. Varrassi G, Pergolizzi JV, Dowling P, Paladini A. Ibuprofen safety at the golden anniversary: are all NSAIDs the same? A narrative review. Advances in therapy. 2020 Jan;37(1):61-82. https://doi.org/10.1007/s12325-019-01144-9
8. Fouad YM, Yehia R. Hepato-cardiac disorders. World journal of hepatology. 2014 Jan 27;6(1):41. https://doi.org/10.4254/wjh.v6.i1.41
9. Clowes JA, Riggs BL, Khosla S. The role of the immune system in the pathophysiology of osteoporosis. Immunological reviews. 2005 Dec;208(1):207-27. https://doi.org/10.1111/j.0105-2896.2005.00334.x
10. Balogun TA, Ige OM, Alausa AO, Onyeani CO, Tiamiyu ZA, Omoboyowa DA, Saibu OA, Abdullateef OT. Receptor tyrosine kinases as a therapeutic target by natural compounds in cancer treatment. Future Journal of Pharmaceutical Sciences. 2021 Dec;7:1-5. https://doi.org/10.1186/s43094-021-00346-9
11. Shimizu M, Weinstein IB. Modulation of signal transduction by tea catechins and related phytochemicals. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2005 Dec 11;591(1-2):147-60. https://doi.org/10.1016/j.mrfmmm.2005.04.010
12. Liu X, Xiao X, Han X, Yao L, Lan W. A new therapeutic trend: natural medicine for ameliorating ischemic stroke via PI3K/Akt signaling pathway. Molecules. 2022 Nov 17;27(22):7963. https://doi.org/10.3390/molecules27227963
13. Gupta R, Panwar RB, Sharma A, Panwar SR, Rao RS, Gupta BK. Continuing burden of rheumatic heart disease in India. J Assoc Physicians India. 2020 Oct 1;68(10):60-5.
14. Palsra P, Raman Gupta DJ, Devi N, Dhiman S. RHEUMATOID ARTHRITIS: A REVIEW.
15. Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. Pharmacoeconomics. 2014 Sep;32:841-51. https://doi.org/10.1007/s40273-014-0174-6
16. Aral SO, Holmes KK. The epidemiology of STIs and their social and behavioral determinants: industrialized and developing countries. Sexually Transmitted Diseases, 4th 3ed. New York: McGraw-Hill. 2008:53-92.
17. Favalli EG, Biggioggero M, Crotti C, Becciolini A, Raimondo MG, Meroni PL. Sex and management of rheumatoid arthritis. Clinical reviews in allergy & immunology. 2019 Jun 15;56:333-45. https://doi.org/10.1007/s12016-018-8672-5
18. Elders MJ. The increasing impact of arthritis on public health. The Journal of Rheumatology. Supplement. 2000 Oct 1;60:6-8.
19. Shrivastava AK, Pandey A. Inflammation and rheumatoid arthritis. Journal of physiology and biochemistry. 2013 Jun;69:335-47. https://doi.org/10.1007/s13105-012-0216-5
20. Ainola M. Pannus invasion into cartilage and bone in rheumatoid arthritis.
21. ur Rehman S, Iqbal S, Shahid MU, Jahangir MS, Malik AL. Cartilage: structure, function, and the pathogenesis of osteoarthritis. InAdvancements in Synovial Joint Science-Structure, Function, and Beyond 2024 Jan 23. IntechOpen. https://doi.org/10.5772/intechopen.1003264
22. Buckwalter JA, Anderson DD, Brown TD, Tochigi Y, Martin JA. The roles of mechanical stresses in the pathogenesis of osteoarthritis: implications for treatment of joint injuries. Cartilage. 2013 Oct;4(4):286-94. https://doi.org/10.1177/1947603513495889
23. Cancedda R. Cartilage and bone extracellular matrix. Current pharmaceutical design. 2009 Apr 1;15(12):1334-48. https://doi.org/10.2174/138161209787846739
24. Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, Zheng MH. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. Arthritis research & therapy. 2013 Dec;15:1-2. https://doi.org/10.1186/ar4405
25. Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection. Cytokine. 2014 Dec 1;70(2):185-93. https://doi.org/10.1016/j.cyto.2014.06.019
26. Shrivastava AK, Pandey A. Inflammation and rheumatoid arthritis. Journal of physiology and biochemistry. 2013 Jun;69:335-47. https://doi.org/10.1007/s13105-012-0216-5
27. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best practice & research Clinical rheumatology. 2017 Feb 1;31(1):3-18. https://doi.org/10.1016/j.berh.2017.08.003
28. Wysocki T, Olesińska M, Paradowska-Gorycka A. Current understanding of an emerging role of HLA-DRB1 gene in rheumatoid arthritis-from research to clinical practice. Cells. 2020 May 2;9(5):1127. https://doi.org/10.3390/cells9051127
29. Hui LY. Localisation of Citrullinated and Carbamylated Proteins in the Inflamed Gingival Tissues of Rheumatoid Arthritis (Master's thesis, University of Malaya (Malaysia)).
30. Sokolova M. The Role of IgA Anti-Citrullinated Protein Antibodies (ACPA) in Rheumatoid Arthritis and Glycosylation Differences of IgA Subclasses. Friedrich-Alexander-Universitaet Erlangen-Nuernberg (Germany); 2023.
31. Shaikh PZ. Cytokines & their physiologic and pharmacologic functions in inflammation: A review. International Journal of Pharmacy & Life Sciences. 2011 Nov 1;2(11).
32. Sanchez-Lopez E, Coras R, Torres A, Lane NE, Guma M. Synovial inflammation in osteoarthritis progression. Nature Reviews Rheumatology. 2022 May;18(5):258-75. https://doi.org/10.1038/s41584-022-00749-9
33. Mukherjee A, Das B. The role of inflammatory mediators and matrix metalloproteinases (MMPs) in the progression of

osteoarthritis. Biomaterials and Biosystems. 2024 Feb 21:100090. https://doi.org/10.1016/j.bbiosy.2024.100090

34. Spondyloarthropathies S, Arthropathies CI. Alterations in the Skeletal System: Metabolic and Rheumatoid Disorders.

35. Ciesielski O, Biesiekierska M, Panthu B, Soszyński M, Pirola L, Balcerczyk A. Citrullination in the pathology of inflammatory and autoimmune disorders: recent advances and future perspectives. Cellular and Molecular Life Sciences. 2022 Feb;79(2):94. https://doi.org/10.1007/s00018-022-04126-3

36. Kaur B, Singh P. Inflammation: Biochemistry, cellular targets, anti-inflammatory agents and challenges with special emphasis on cyclooxygenase-2. Bioorganic Chemistry. 2022 Apr 1;121:105663. https://doi.org/10.1016/j.bioorg.2022.105663

37. Silva LC, Ortigosa LC, Benard G. Anti-TNF-α agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. Immunotherapy. 2010 Nov 1;2(6):817-33. https://doi.org/10.2217/imt.10.67

38. Kesharwani D, Paliwal R, Satapathy T, Paul SD. Rheumatiod arthritis: an updated overview of latest therapy and drug delivery. Journal of pharmacopuncture. 2019 Dec 31;22(4):210. https://doi.org/10.3831/KPI.2019.22.029

39. Roy K, Kanwar RK, Kanwar JR. Molecular targets in arthritis and recent trends in nanotherapy. International journal of nanomedicine. 2015 Aug 26:5407-20. https://doi.org/10.2147/IJN.S89156

40. Ha H, Debnath B, Neamati N. Role of the CXCL8-CXCR1/2 axis in cancer and inflammatory diseases. Theranostics. 2017 Apr 7;7(6):1543. https://doi.org/10.7150/thno.15625

41. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochemical and biophysical research communications. 2004 Oct 15;323(2):630-5. https://doi.org/10.1016/j.bbrc.2004.08.145

42. Cawston TE, Young DA. Proteinases involved in matrix turnover during cartilage and bone breakdown. Cell and tissue research. 2010 Jan;339:221-35. https://doi.org/10.1007/s00441-009-0887-6

43. Ooka S, Kurokawa MS, Yokoyama M, Arito M, Sato T, Sato M, Takakuwa Y, Omoteyama K, Suematsu N, Kawahata K, Kato T. Effects of iguratimod on protein profiles of chondrosarcoma cells. Integr. Mol. Med.. 2017 Dec 14;4:1-8. https://doi.org/10.15761/IMM.1000315

44. Gerstenfeld LC, Einhorn TA. COX inhibitors and their effects on bone healing. Expert opinion on drug safety. 2004 Mar 1;3(2):131-6. https://doi.org/10.1517/14740338.3.2.131

45. Gizinski AM, Fox DA, Sarkar S. Co-stimulation and T cells as therapeutic targets. Best Practice & Research Clinical Rheumatology. 2010 Aug 1;24(4):463-77. https://doi.org/10.1016/j.berh.2009.12.015

46. Mrid RB, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. Biomedicine & Pharmacotherapy. 2022 Jul 1;151:113126. https://doi.org/10.1016/j.biopha.2022.113126

47. Drosos AA, Pelechas E, Voulgari PV. Conventional radiography of the hands and wrists in rheumatoid arthritis. What a rheumatologist should know and how to interpret the radiological findings. Rheumatology international. 2019 Aug 1;39(8):1331-41. https://doi.org/10.1007/s00296-019-04326-4

48. Sarkar PK, Hossain N, Nahid M, Alam J. Disease Modifying Anti-rheumatic Drugs (DMARDs). Bangladesh Journal of Child Health. 2018 Jul 31;42(2):79-85. https://doi.org/10.3329/bjch.v42i2.37763

49. Pawar AT, Baheti AM, Adate-More P, Upaganlawar A. Conventional Therapy for Rheumatoid Arthritis. Natural Products for the Management of Arthritic Disorders. 2020;26:2962-70. https://doi.org/10.2174/978981505077612201004

50. Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, Ralandison S, Gasque P. Methotrexate an old drug with new tricks. International journal of molecular sciences. 2019 Oct 10;20(20):5023. https://doi.org/10.3390/ijms20205023

51. Choi J, Patel P, Fenando A. Sulfasalazine. InStatPearls [Internet] 2024 Mar 21. StatPearls Publishing. https://doi.org/10.1080/15424065.2024.2389325

52. Pasquini S, Contri C, Borea PA, Vincenzi F, Varani K. Adenosine and inflammation: here, there and everywhere. International journal of molecular sciences. 2021 Jul 19;22(14):7685. https://doi.org/10.3390/ijms22147685

53. Martinez GP, Zabaleta ME, Di Giulio C, Charris JE, Mijares MR. The role of chloroquine and hydroxychloroquine in immune regulation and diseases. Current pharmaceutical design. 2020 Oct 1;26(35):4467-85. https://doi.org/10.2174/1381612826666200707132920

54. Pawar AT, Baheti AM, Adate-More P, Upaganlawar A. Conventional Therapy for Rheumatoid Arthritis. Natural Products for the Management of Arthritic Disorders. 2020;26:2962-70. https://doi.org/10.2174/978981505077612201004

55. Catrina AI. Studies of molecular mechanisms of action of TNF antagonists in rheumatoid arthritis. Karolinska Institutet; 2004 Nov 26.

56. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Mola EM, Pavelka K, Sany J, Settas L, Wajdula J. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet. 2004 Feb 28;363(9410):675-81. https://doi.org/10.1016/S0140-6736(04)15640-7

57. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, Miranda P, Park MC, Pavelka K, Pedersen R, Szumski A. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. The Lancet. 2013 Mar 16;381(9870):918-29. https://doi.org/10.1016/S0140-6736(12)61811-X

58. Pawar AT, Baheti AM, Adate-More P, Upaganlawar A. Conventional Therapy for Rheumatoid Arthritis. Natural Products for the Management of Arthritic Disorders. 2020;26:2962-70. https://doi.org/10.2174/978981505077612201004

59. Vardanyan M, Parkin EC, Rodriguez Rilo HL. Infliximab/Anti-TNF. Immunotherapy in Transplantation: Principles and Practice. 2010 Apr 16:385-98. https://doi.org/10.1002/9781444355628.ch26

60. Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. Journal of pharmacy & pharmaceutical sciences. 2008 Sep 20;11(2):81s-110s. https://doi.org/10.18433/J3T886

61. Sakamoto C. Roles of COX-1 and COX-2 in gastrointestinal pathophysiology. Journal of gastroenterology. 1998 Sep;33:618-24. https://doi.org/10.1007/s005350050147

62. Grosser T, Smyth E, FitzGerald GA. Anti-inflammatory, antipyretic, and analgesic agents; pharmacotherapy of gout. Goodman and Gilman's the pharmacological basis of therapeutics. 2011;12:959-1004.

63. Sharma JN, Jawad NM. Adverse effects of COX-2 inhibitors. The Scientific World Journal. 2005;5(1):629-45. https://doi.org/10.1100/tsw.2005.82

64. Mrid RB, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. Biomedicine & Pharmacotherapy. 2022 Jul 1;151:113126. https://doi.org/10.1016/j.biopha.2022.113126

65. Chikanza IC, Kozaci DL. Corticosteroid resistance in rheumatoid arthritis: molecular and cellular perspectives. Rheumatology. 2004 Nov 1;43(11):1337-45. https://doi.org/10.1093/rheumatology/keh333

66. Cadena DL, Gill GN. Receptor tyrosine kinases. The FASEB Journal. 1992 Mar;6(6):2332-7 https://doi.org/10.1096/fasebj.6.6.1312047

67. Roskoski Jr R. The ErbB/HER family of protein-tyrosine kinases and cancer. Pharmacological research. 2014 Jan 1;79:34-74. https://doi.org/10.1016/j.phrs.2013.11.002

68. Stuttfeld E, Ballmer-Hofer K. Structure and function of VEGF receptors. IUBMB life. 2009 Sep;61(9):915-22. https://doi.org/10.1002/iub.234

69. Grassot J, Gouy M, Perrière G, Mouchiroud G. Origin and molecular evolution of receptor tyrosine kinases with immunoglobulin-like domains. Molecular biology and evolution. 2006 Jun 1;23(6):1232-41. https://doi.org/10.1093/molbev/msk007

70. Ségaliny AI, Tellez-Gabriel M, Heymann MF, Heymann D. Receptor tyrosine kinases: Characterisation, mechanism of action and therapeutic interests for bone cancers. Journal of bone oncology. 2015 Mar 1;4(1):1-2. https://doi.org/10.1016/j.jbo.2015.01.001

71. Ségaliny AI, Tellez-Gabriel M, Heymann MF, Heymann D. Receptor tyrosine kinases: Characterisation, mechanism of action and therapeutic interests for bone cancers. Journal of bone oncology. 2015 Mar 1;4(1):1-2. https://doi.org/10.1016/j.jbo.2015.01.001

72. Tsygankov AY. Non-receptor protein tyrosine kinases. Front Biosci. 2003 May 1;8(6):S595-635. https://doi.org/10.2741/1106

73. Okada M. Regulation of the SRC family kinases by Csk. International journal of biological sciences. 2012 Nov 1;8(10):1385. https://doi.org/10.7150/ijbs.5141

74. Roskoski Jr R. Src protein-tyrosine kinase structure and regulation. Biochemical and biophysical research communications. 2004 Nov 26;324(4):1155-64. https://doi.org/10.1016/j.bbrc.2004.09.171

75. Yang WC, Ching KA, Tsoukas CD, Berg LJ. Tec kinase signaling in T cells is regulated by phosphatidylinositol 3-kinase and the Tec pleckstrin homology domain. The Journal of Immunology. 2001 Jan 1;166(1):387-95. https://doi.org/10.4049/jimmunol.166.1.387

76. Bradshaw JM. The Src, Syk, and Tec family kinases: distinct types of molecular switches. Cellular signalling. 2010 Aug 1;22(8):1175-84. https://doi.org/10.1016/j.cellsig.2010.03.001

77. Shi S. Assessment of turmeric (Curcuma longa L.) varieties for yield and curcumin content (Master's thesis, Auburn University).

78. Mateen S, Zafar A, Moin S, Khan AQ, Zubair S. Understanding the role of cytokines in the pathogenesis of rheumatoid arthritis. Clinica chimica acta. 2016 Apr 1;455:161-71. https://doi.org/10.1016/j.cca.2016.02.010

79. Balogh E. Downstream effects of targeting angiogenesis in the inflamed joint and systemic vasculature in inflammatory arthritis. PQDT-Global. 2019.

80. Shah M. Cutaneous scarring: Modulation by transforming growth factor-beta and its antagonists. The University of Manchester (United Kingdom); 1993.

81. Hung CY, Hsueh TY, Rethi L, Lu HT, Chuang AE. Advancements in regenerative medicine: a comprehensive review of stem cell and growth factor therapies for osteoarthritis. Journal of Materials Chemistry B. 2025. https://doi.org/10.1039/D4TB01769B

82. Bilski R, Nuszkiewicz J. Antioxidant Therapies as Emerging Adjuncts in Rheumatoid Arthritis: Targeting Oxidative Stress to Enhance Treatment Outcomes. International Journal of Molecular Sciences. 2025 Jan;26(7):2873. https://doi.org/10.3390/ijms26072873

83. Kumar A, Chopra K, Mukherjee M, Pottabathini R, Dhull DK. Current knowledge and pharmacological profile of berberine: an update. European journal of pharmacology. 2015 Aug 15;761:288-97. https://doi.org/10.1016/j.ejphar.2015.05.068

84. Sivasakthi P, Sanmuga Priya E, Senthamil Selvan PJ. Molecular insights into phytochemicals exhibiting anti-arthritic activity: Systematic review: John Di Battista. Inflammation Research. 2021 Jun;70(6):665-85. https://doi.org/10.1007/s00011-021-01471-0

85. Yang L, Wang NL, Cai GP. Maohuoside A promotes osteogenesis of rat mesenchymal stem cells via BMP and MAPK signaling pathways. Molecular and cellular biochemistry. 2011 Dec;358:37-44. https://doi.org/10.1007/s11010-011-0918-y

86. Wang X, Liu E, Hou C, Wang Y, Zhao Y, Guo J, Li M. Effects of natural products on angiogenesis in melanoma. Fitoterapia. 2024 Jul 6:106100. https://doi.org/10.1016/j.fitote.2024.106100

87. Szczuka D, Nowak A, Zakłos-Szyda M, Kochan E, Szymańska G, Motyl I, Blasiak J. American ginseng (Panax quinquefolium L.) as a source of bioactive phytochemicals with pro-health properties. Nutrients. 2019 May 9;11(5):1041. https://doi.org/10.3390/nu11051041

88. Jang WY, Hwang JY, Cho JY. Ginsenosides from Panax ginseng as key modulators of NF-κB signaling are powerful anti-inflammatory and anticancer agents. International Journal of Molecular Sciences. 2023 Mar 24;24(7):6119. https://doi.org/10.3390/ijms24076119

89. Ivanenkov YA, Balakin KV, Lavrovsky Y. Small molecule inhibitors of NF-kB and JAK/STAT signal transduction pathways as promising anti-inflammatory therapeutics. Mini Rev Med Chem. 2011 Jan 1;11(1):55-78. https://doi.org/10.2174/138955711793564079

90. Chen JY, Tian XY, Wei SS, Yang YJ, Deng S, Jiao CJ, Wang CJ, Chu KD, Ma XQ, Xu W. Perspectives of herbs and their natural compounds, and herb formulas on treating diverse diseases through regulating complicated JAK/STAT signaling. Frontiers in Pharmacology. 2022 Oct 17;13:993862. https://doi.org/10.3389/fphar.2022.993862

91. Sarkar J, Das M, Howlader MS, Prateeksha P, Barthels D, Das H. Epigallocatechin-3-gallate inhibits osteoclastic differentiation by modulating mitophagy and mitochondrial functions. Cell death & disease. 2022 Oct 28;13(10):908. https://doi.org/10.1038/s41419-022-05343-1

92. Riegsecker S, Wiczynski D, Kaplan MJ, Ahmed S. Potential benefits of green tea polyphenol EGCG in the prevention and treatment of vascular inflammation in rheumatoid arthritis. Life sciences. 2013 Sep 3;93(8):307-12. https://doi.org/10.1016/j.lfs.2013.07.006

93. Song C, Xu S, Chang L, Zhao X, Mei X, Ren X, Chen Z. Preparation of EGCG decorated, injectable extracellular vesicles for cartilage repair in rat arthritis. Regenerative biomaterials. 2021 Dec 1;8(6):rbab067. https://doi.org/10.1093/rb/rbab067

94. Malemud CJ. Growth hormone, VEGF and FGF: involvement in rheumatoid arthritis. Clinica chimica acta. 2007 Jan 1;375(1-2):10-9. https://doi.org/10.1016/j.cca.2006.06.033

95. Wang X, Liu E, Hou C, Wang Y, Zhao Y, Guo J, Li M. Effects of natural products on angiogenesis in melanoma. Fitoterapia. 2024 Jul 6:106100. https://doi.org/10.1016/j.fitote.2024.106100

96. Kashyap VK, Peasah-Darkwah G, Dhasmana A, Jaggi M, Yallapu MM, Chauhan SC. Withaniasomnifera: progress towards a pharmaceutical agent for immunomodulation and cancer therapeutics. Pharmaceutics. 2022 Mar 10;14(3):611. https://doi.org/10.3390/pharmaceutics14030611

97. D'Aura Swanson C, Paniagua RT, Lindstrom TM, Robinson WH. Tyrosine kinases as targets for the treatment of rheumatoid arthritis. Nature Reviews Rheumatology. 2009 Jun;5(6):317-24. https://doi.org/10.1038/nrrheum.2009.82

98. Patidar V, Shah S, Kumar R, Singh PK, Singh SB, Khatri DK. A molecular insight of inflammatory cascades in rheumatoid arthritis and anti-arthritic potential of phytoconstituents. Molecular Biology Reports. 2022 Mar 1:1-7.

99. Shah AA, Gupta A. Phytochemicals and novel nanotherapeutic approaches in the management of rheumatic diseases. InInnovative Approaches for Nanobiotechnology in Healthcare Systems 2022 (pp. 249-266). IGI Global Scientific Publishing. https://doi.org/10.4018/978-1-7998-8251-0.ch009

100. Devikar SD, Naikawadi VB, Shirke HA, Aher RK, Nikam TD, Naikawadi VB. Regeneration through somatic embryogenesis from zygotic embryo explant of Boswellia serrata Roxb. and detection of medicinal boswellic acid.

101. Hongzhi D, Xiaoying H, Yujie G, Le C, Yuhuan M, Dahui L, Luqi H. Classic mechanisms and experimental models for the anti-inflammatory effect of traditional Chinese medicine. Animal Models and Experimental Medicine. 2022 Apr;5(2):108-19. https://doi.org/10.1002/ame2.12224

102. Mioc M, Prodea A, Racoviceanu R, Mioc A, Ghiulai R, Milan A, Voicu M, Mardale G, Șoica C. Recent advances regarding the molecular mechanisms of triterpenic acids: A review (part II). International Journal of Molecular Sciences. 2022 Aug 10;23(16):8896. https://doi.org/10.3390/ijms23168896

103. Ammon HP. Boswellic acids and their role in chronic inflammatory diseases. Anti-inflammatory Nutraceuticals and Chronic Diseases. 2016:291-327. https://doi.org/10.1007/978-3-319-41334-1_13

104. Dixon RA, Ferreira D. Genistein. Phytochemistry. 2002 Jun 1;60(3):205-11. https://doi.org/10.1016/S0031-9422(02)00116-4

105. Peng Q, Li Y, Shang J, Huang H, Zhang Y, Ding Y, Liang Y, Xie Z, Chen C. Effects of genistein on common kidney diseases. Nutrients. 2022 Sep 13;14(18):3768. https://doi.org/10.3390/nu14183768

106. Sharifi-Rad J, Quispe C, Imran M, Rauf A, Nadeem M, Gondal TA, Ahmad B, Atif M, Mubarak MS, Sytar O, Zhilina OM. Genistein: an integrative overview of its mode of action, pharmacological properties, and health benefits. Oxidative medicine and cellular longevity. 2021;2021(1):3268136. https://doi.org/10.1155/2021/3268136

107. Goh YX, Jalil J, Lam KW, Husain K, Premakumar CM. Genistein: A review on its anti-inflammatory properties. Frontiers in pharmacology. 2022 Jan 24;13:820969. https://doi.org/10.3389/fphar.2022.820969

108. Sulaiman MK. Molecular mechanisms and therapeutic potential of natural flavonoids in diabetic nephropathy: Modulation of intracellular developmental signaling pathways. Current Research in Pharmacology and Drug Discovery. 2024 Jul 3:100194. https://doi.org/10.1016/j.crphar.2024.100194

109. Javed Z, Khan K, Herrera-Bravo J, Naeem S, Iqbal MJ, Sadia H, Qadri QR, Raza S, Irshad A, Akbar A, Reiner Ž. Genistein as a regulator of signaling pathways and microRNAs in different types of cancers. Cancer Cell International. 2021 Dec;21:1-2. https://doi.org/10.1186/s12935-021-02091-8

110. Frémont L. Biological effects of resveratrol. Life sciences. 2000 Jan 14;66(8):663-73. https://doi.org/10.1016/S0024-3205(99)00410-5

111. Ba X, Huang Y, Shen P, Huang Y, Wang H, Han L, Lin WJ, Yan HJ, Xu LJ, Qin K, Chen Z. WTD attenuating rheumatoid arthritis via suppressing angiogenesis and modulating the PI3K/AKT/mTOR/HIF-1α pathway. Frontiers in Pharmacology. 2021 Sep 27;12:696802. https://doi.org/10.3389/fphar.2021.696802

112. Yang G, Chang CC, Yang Y, Yuan L, Xu L, Ho CT, Li S. Resveratrol alleviates rheumatoid arthritis via reducing ROS and inflammation, inhibiting MAPK signaling pathways, and suppressing angiogenesis. Journal of agricultural and food chemistry. 2018 Dec 4;66(49):12953-60. https://doi.org/10.1021/acs.jafc.8b05047

113. Li Q, Chen Y, Liu H, Tian Y, Yin G, Xie Q. Targeting glycolytic pathway in fibroblast-like synoviocytes for rheumatoid arthritis therapy: challenges and opportunities. Inflammation Research. 2023 Dec;72(12):2155-67. https://doi.org/10.1007/s00011-023-01807-y

114. Byun JY, Koh YT, Jang SY, Witcher JW, Chan JR, Pustilnik A, Daniels MJ, Kim YH, Suh KH, Linnik MD, Lee YM. Target modulation and pharmacokinetics/pharmacodynamics translation of the BTK inhibitor poseltinib for model-informed phase II dose selection. Scientific Reports. 2021 Sep 21;11(1):18671. https://doi.org/10.1038/s41598-021-98255-7

115. Tavakoli GM, Yazdanpanah N, Rezaei N. Targeting Bruton's tyrosine kinase (BTK) as a signaling pathway in immune-mediated diseases: from molecular mechanisms to leading treatments. Advances in Rheumatology. 2024 Sep 30;64:61. https://doi.org/10.1186/s42358-024-00401-y

116. Dong XD, Lu Q, Li YD, Cai CY, Teng QX, Lei ZN, Wei ZH, Yin F, Zeng L, Chen ZS. RN486, a Bruton's Tyrosine Kinase inhibitor, antagonizes multidrug resistance in ABCG2-overexpressing cancer cells. Journal of Translational Internal Medicine. 2024 Jul 27;12(3):288-98.

117. Xu D, Kim Y, Postelnek J, Vu MD, Hu DQ, Liao C, Bradshaw M, Hsu J, Zhang J, Pashine A, Srinivasan D. RN486, a selective Bruton's tyrosine kinase inhibitor, abrogates immune hypersensitivity responses and arthritis in rodents. The Journal of pharmacology and experimental therapeutics. 2012 Apr 1;341(1):90-103. https://doi.org/10.1124/jpet.111.187740

118. Xu D, Kim Y, Postelnek J, Vu MD, Hu DQ, Liao C, Bradshaw M, Hsu J, Zhang J, Pashine A, Srinivasan D. RN486, a selective Bruton's tyrosine kinase inhibitor, abrogates immune hypersensitivity responses and arthritis in rodents. The Journal of pharmacology and experimental therapeutics. 2012 Apr 1;341(1):90-103. https://doi.org/10.1124/jpet.111.187740

119. D'Aura Swanson C, Paniagua RT, Lindstrom TM, Robinson WH. Tyrosine kinases as targets for the treatment of rheumatoid arthritis. Nature Reviews Rheumatology. 2009 Jun;5(6):317-24. https://doi.org/10.1038/nrrheum.2009.82

120. Baradaran Rahimi V, Askari VR, Hosseinzadeh H. Promising influences of Scutellaria baicalensis and its two active constituents, baicalin, and baicalein, against metabolic syndrome: A review. Phytotherapy research. 2021 Jul;35(7):3558-74. https://doi.org/10.1002/ptr.7046

121. Ye Z, Liu Y, Song J, Gao Y, Fang H, Hu Z, Zhang M, Liao W, Cui L, Liu Y. Expanding the therapeutic potential of Salvia miltiorrhiza: a review of its pharmacological applications in musculoskeletal diseases. Frontiers in Pharmacology. 2023 Dec 5;14:1276038. https://doi.org/10.3389/fphar.2023.1276038

122. Lee HE, Yang G, Han SH, Lee JH, An TJ, Jang JK, Lee JY. Anti-obesity potential of Glycyrrhiza uralensis and licochalcone A through induction of adipocyte browning. Biochemical and Biophysical Research Communications. 2018 Sep 10;503(3):2117-23. https://doi.org/10.1016/j.bbrc.2018.07.168

123. Ma J, Dey M, Yang H, Poulev A, Pouleva R, Dorn R, Lipsky PE, Kennelly EJ, Raskin I. Anti-inflammatory and immunosuppressive compounds from Tripterygium wilfordii. Phytochemistry. 2007 Apr 1;68(8):1172-8. https://doi.org/10.1016/j.phytochem.2007.02.021

124. Tong X, Wang Y, Dong B, Li Y, Lang S, Ma J, Ma X. Effects of genus Epimedium in the treatment of osteoarthritis and relevant signaling pathways. Chinese Medicine. 2023 Jul 31;18(1):92. https://doi.org/10.1186/s13020-023-00788-8

125. Chen P, Zhou J, Ruan AM, Ma YF, Wang QF. Paeoniflorin, the Main monomer component of paeonia lactiflora, exhibits anti-inflammatory properties in osteoarthritis synovial inflammation. Chinese Journal of Integrative Medicine. 2024 May;30(5):433-42. https://doi.org/10.1007/s11655-023-3653-9

126. Wu L, Yang Y, Mao Z, Wu J, Ren D, Zhu B, Qin L. Processing and compatibility of Corydalis yanhusuo: phytochemistry, pharmacology, pharmacokinetics, and safety. Evidence-Based Complementary and Alternative Medicine. 2021;2021(1):1271953. https://doi.org/10.1155/2021/1271953

127. Ran X, Ma L, Peng C, Zhang H, Qin LP. Ligusticum chuanxiong Hort: a review of chemistry and pharmacology. Pharmaceutical Biology. 2011 Nov 1;49(11):1180-9. https://doi.org/10.3109/13880209.2011.576346