Role of phytochemical constituents and its therapeutic application for the treatment of Rheumatoid Arthritis

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***Abstract*- Rheumatoid arthritis (RA) is a chronic, inflammatory, Autoimmune disorder , affecting the joints . The risk factors include genetics, and environmental factors like cigarette smoking, air pollutants. As there is no cure for RA, and the medications used to treat rheumatoid arthritis must be taken for longer than six months, and they can have a number of negative effects, including gastrointestinal disorders, immunodeficiency, humoral disturbances, cardiovascular problems, etc. Moreover, the treatment goals are only to reduce the pain and slows further damage from cartilage destruction and bone deformities. Here, we present a brief summary of various Phytoconstituents and their mechanism of action to address the complications associated with RA.**

Keywords: **Auto immune disorder, Phytoconstituents, Rheumatoid arthritis, NF-κB pathway, MAP kinase.**

1. INTRODUCTION

One of the body's primary defence mechanisms against external stimuli, such as an injury or infection caused by a pathogen, is inflammation. An immunological response that is essential for the body to survive an injury is inflammation. There are two primary categories of inflammation: acute and chronic (1). Inflammation is a complicated process that involves many cellular interactions. Acute inflammation provide protection to the body by increase the immune system whereas chronic inflammation cause damage to the body like cardiovascular disease, skeletal muscle disorders, inflammatory bowel disease, diabetes, cancer, and neurological diseases. People who have rheumatoid arthritis (RA) frequently state that pain is their main concern. Pain can worsen physical and social functioning, be linked to psychological discomfort, and lead to more people seeking medical attention (2).

Over time, rheumatoid arthritis (RA) can affect the skin, eyes, heart, kidneys, and lungs. It is a symmetrical, inflammatory, chronic autoimmune disease that starts in small joints and becomes larger. In many cases, tendons and ligaments deteriorate and joint bone and cartilage are lost. The common symptoms of Rheumatoid arthritis is Rheumatoid nodules under the skin, weariness, fever, weight loss, sensitive, swollen, and heated joints, and morning stiffness of the affected joints lasting more than thirty minutes. (3). Early RA is characterized by symptoms that present for six months, while established RA is defined by symptoms that present for more than six months. Untreated RA is a progressive illness that increases morbidity and mortality. (4). Rheumatoid arthritis (RA) is twice as common in women as in males, and it is thought to afflict 0.24 to 1 percent of the population usually at the age of 35 to 60 years. According to the Global Burden of Disease 2010 Study, the estimated prevalence of RA worldwide is 0.24 percent. In northern Europe and the United States, estimates of RA prevalence are generally higher, ranging from 0.5 to 1 percent. (5).

Reducing disability, easing pain, and controlling inflammation are the basic objectives of treatment for rheumatoid arthritis. Medication, physical therapy, exercise, and surgery are often used forms of treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and disease-modifying antirheumatic drugs (DMARDs) are some of the medications used to treat the pain and inflammation associated with RA. Sometimes taking additional medications is necessary to lessen the potential side effects of taking RA medication. The drug can lessen discomfort, but it cannot totally reverse the illness. (6)

Preclinical studies conducted recently have demonstrated the considerable reduction of RA that can be achieved using natural plant extracts and phytoconstituents. Patients with less adverse effects will benefit from the phytoconstituents for RA treatment, which offer a variety of intricate activities. As a result, we discuss the latest developments in phytoconstituent research as a RA treatment here. (7)

2. POLY PHENOLS

Fruits, vegetables, tea, dark chocolate, spices, herbs, and wine are examples of plant foods that naturally contain polyphenols. Since they have the ability to neutralize damaging free radicals, they can work as antioxidants, reducing the risk of heart disease, diabetes, cancer, and other illnesses as well as causing damage to your cells. It's also believed

that polyphenols lessen inflammation, which is the main culprit behind a lot of chronic illnesses. (8). The list of poly phenols are as follows

2.1. Catechins

The term "Catechin," which comes from the catechu of the Acacia catechu L. extract, refers to a 3,3',4',5,7-pentahydroxyflavan that has two steric forms of (+)-catechin and its enantiomer. Tea, apples, persimmons, cacao, grapes, berries, and grapes are just a few of the foods and herbs that contain catechins. (9). Generally speaking, the primary components of catechins include EGCG and its stereoisomer Gallo catechin gallate (GCG), epigallocatechin (EGC) and its stereoisomer Gallo catechin (GC), epicatechin (EC), epicatechin gallate (ECG), and catechin. Their compositions are comparable to one another. Catechins can demonstrate their potent anti-inflammatory effects by controlling the activation or deactivation of oxidative stress-related cell signalling pathways that are related to inflammation, such as mitogen-activated protein kinases (MAPKs), transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), signal transducer, and the activator of transcription 1/3 (STAT1/3) pathways(10).catechins present in green tea specifically disrupt the IL-1β signalling pathway, which controls the production of Cox-2 and pro-inflammatory mediators (IL-6 and IL-8) in primary human rheumatoid arthritis synovial fibroblasts (RASFs).(11)and prevent the bone degradation.

2.2. Ellagic acid

Ellagic acid (EA) is a naturally occurring secondary metabolite of bioactive polyphenolic compounds found in a wide variety of plant. The pomegranate (Punica granatum L.), as well as the wood and bark of certain tree species, contain a significant amount of EA. In terms of structure, EA is a dilactone of hexahydroxy diphenic acid (HHDP), a dimeric derivative of gallic acid that is mostly generated through the hydrolysis of ellagitannins, a class of secondary metabolites that are extensively dispersed (12). Ellagic acid inhibits the nuclear translocation of p65 and p50 caused by IL-1β and modifies NF-κB activity to mediate its anti-inflammatory actions. EA affects the production of pro- and anti-inflammatory cytokines, according to several studies (13). Ellagic acid also have antioxidant, antiproliferative, chemo-preventive, and anti-atherogenic, anti - depressant and anti neuro inflammatory properties. Tumour necrosis factor-α (TNF-α), interleukin 17 (IL-17), and interleukin 1β (IL-1β) were the three pro-inflammatory cytokines that ellagic acid significantly ($p < 0.01$) decreased in serum levels. Serum levels of transforming growth factor β (TGF-β) did not significantly change with EA therapy, whereas those of IL-10 and interferon γ (IFN-γ) increased significantly ($p < 0.01$ and $p < 0.05$, respectively) in adjuvant induced mice model. (14).

2.3. Resveratrol

Resveratrol is a polyphenolic molecule that is most convincingly found in a wide range of fruits and vegetables, such as peanuts, grapes, and peanut sprouts. It was originally extracted from plants commonly referred to as white hellebore, or Veratrum grandiflorum. It helps lessen inflammation and oxidative stress, two conditions that extend the lifespan of a variety of animals. Recent studies have shown that improving blood glucose and insulin resistance in diabetics can also prevent obesity (15). It was shown that RES decreased the inflammatory response in chondrocytes; a potential mechanism for this effect could be partial suppression of the NF-kB pathway induced by IL-1β. When chondrocytes and macrophages were co-exposed to an inflammatory environment, Limagne et al. found that RES inhibited the inflammatory growth of NF-kB/STAT3 between the two types of cells(16).Resveratrol has been reported to more successfully inhibit lymphocytes from producing IL-2 and interferon-gamma (IFN-γ) and macrophages from producing tumour necrosis factor alpha (TNF-α) or IL-12, as well as to suppress the proliferation of spleen cells induced by concanavalin A (ConA), interleukin (IL)-2, or allo -antigens . It has been discovered that resveratrol down-regulates the mRNA expression and protein release of IL-17 in vitro and induces a dose-dependent inhibition of the production of IL-1α, IL-6, and TNF-α. (17)

3.0. FLAVANOIDS

Phytochemicals called flavonoids can be found in a wide variety of plants, fruits, vegetables, and leaves. They may have uses in medical chemistry. Flavonoids are beneficial to medicine because of their antiviral, anticancer, antioxidant, and anti-inflammatory qualities. (18)

3.1Quercetin

Plant pigment quercetin, which is mostly present in onions, grapes, berries, cherries, broccoli, and citrus fruits, is a strong antioxidant flavonoid, or more precisely, a flavanol. It is a multipurpose antioxidant with the ability to shield tissue against damage brought on by a range of medication toxicity. There is proof of the biological effects of plant extracts and phytoconstituents, including their ability to scavenge free radicals, reduce inflammation, and treat hyperlipidaemia and diabetes. (19). Quercetin has the potential to mitigate inflammation indirectly by upregulating the activity of peroxisome proliferator-activated receptor c (PPAR γ), which in turn counteracts the transcriptional activation

of inflammatory genes by NF-κB or activator protein-1 (AP-1). Collectively, these prevent inflammatory cascades from being induced by TNF-α. (20).

3.2 Baicalin

aglycone, baicalein, which have a variety of medicinal uses. (21). Baicalin is widely distributed in leaves and stem bark, while Scutellarin (Lamiaceae) is a prominent component of fruit, root bark, and leaves. Based on their ability to effectively treat rheumatoid arthritis, respiratory conditions, inflammatory bowel diseases, cardiovascular disorders, hepatitis, kidney diseases, and neurodegenerative diseases, baicalin and baicalein have been shown to have anti-inflammatory properties. (22). Baicalin suppresses the expression of multiple proinflammatory cytokines, such as caspase-1, cyclooxygenases-2 (COX-2), inducible nitric oxide synthase (I NOS), Tumour necrosis factor-β (TNF-β), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-γ (TNF-γ). It also inhibits the activation of NF-kB and NLRP3 inflammasomes. (23).

3.3 Naringenin

The flavonoid naringenin is a member of the flavanones subclass. It is present in many fruits, including tomatoes, bergamot, citrus fruits, and other fruits. It can also be found in fruits in the form of glycosides, primarily naringin. This phytochemical has been linked to a number of biological activities, including anti-inflammatory, anticancer, antiviral, antibacterial, antioxidant, and cardioprotective properties (24). Naringenin inhibited the expression of IL-6 and TNF-α, recruited macrophages, and reduced liver inflammation (25).

3.4 Tricin

Monocots like wheat, rice, bamboo, maize, and Sasa quell paertensis contain large distributions of tricin (5,7,4′-trihydroxy-3′,5′-dimethoxyflavone), a renewable and bioactive polyphenolic molecule, in both free and conjugated forms (26). Tricine treatment led to a considerable down-regulation of TNF-α, IL-6, PGE2, and NO generation triggered by LPS. It was discovered that tricin may inhibit the expression of cyclooxygenase, matrix metalloproteinases, and nitric oxide synthase isoforms. (27)

3.5 Biochanin

Red clover is the primary source of biochanin A (BCA), an isoflavone with poor oral absorption and solubility that is known to have a variety of benefits, including anti-inflammatory, Oestrogen -like, and glucose and lipid metabolism modulatory activity, as well as neuroprotective, anti-cancer, and drug interaction effects (28). By blocking the NF-κB and MAPK pathways, as well as the inflammatory markers Tumour necrosis factor-α (TNF-α), IL-8, IL-1, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), biochanin inhibits inflammation brought on by lipopolysaccharides (29).

4.ALKALOID

Alkaloids are organic compounds that are basic and occur in nature that contain at least one nitrogen atom. This connection includes certain related compounds that have neutral or slightly acidic properties (30). Alkaloids come in various forms, such as purines, terpenes, piperidines, and quinoline alkaloids, which vary based on the structure of their ring chains.

4.1 Quinoline

Quinoline alkaloids are heterocyclic aromatic chemicals based on nitrogen that exhibit a wide variety of biological functions. Moreover, a large number of quinoline alkaloids have been found and isolated from natural sources, and various studies have reported on their antiviral, antiplatelet, anticancer, antimalarial, antibacterial, antifungal, antiparasitic, and insecticidal properties (31).

4.1.1 Berberine

Naturally occurring benzyl iso quinoline alkaloid berberine (C20H18NO4 +) is mostly found in the roots, rhizomes, and stem bark of a variety of medicinal plants belonging to the families Rutaceae, Berberidaceae, and Ranunculaceae. Berberine's structure consists of a planar isoquinoline ring and a dihydroisoquinoline ring (32). Treatment with BBR increased the expression of miR23a, which in turn improved the levels of TLR4, TRAF2, TNF-α, IL-6, and IL-23 expression. In addition, BBR can lower the percentage of F4/80+CD11c+ M1 macrophages and prevent RAW264.7 cells triggered by LPS from polarizing (33).

4.1.2 Tetrandine

Stephania tetrandra S. Moore, the Chinese herbal yield tetrandrine (Tet), a dibenzylisoquinoline alkaloid. Tet also has antifibrogenetic qualities in liver or lung fibrosis, whether or not portal or pulmonary hypertension is present, and it is an immunomodulating and anticarcinoma medication (34). Tetrandine may suppress the expression of IL-6, IL-1β, and TNF-α in LPS-stimulated RAW 264.7 cells by preventing the nuclear translocation of nuclear factor (NF)-κB p65 (35).

4.1.3 Sinomenine

The primary active ingredient in these traditional Chinese medicines, which have been used for generations to cure rheumatism and neuralgia, is an alkaloid called somenine, which was extracted from the root and stem of Sinomenium acutum Rehder et Wilson or Sinomenium acutum var. cinereum (36).Tumour necrosis factor (TNF)-α and inflammatory

cytokine levels, such as interleukin (IL)-1β and IL-6, were reduced in lipopolysaccharide (LPS)-stimulated cells when specific genes, including Ripk 3, Ptges3, Prdx4, and Dbnl, were knocked down(37).

4.2 Piperidine alkaloid

4.2.1 Aloperine

The medicinal plant Sophora alopecuroides L. contains the alkaloid aloperine in its seeds and leaves. It has strong anti-inflammatory, antioxidant, antibacterial, and antiviral qualities. (38). Administering aloperine protects against oxidized LDL-induced damage and prevents U937 monocyte adherence to HUVECs by downregulating the expression of E-selectin, MCP-1, VCAM-1, and IL-6. The advantageous effects of aloperine may possibly be attributed to reduced oxidative stress (39).

4.2.2 Matrine

Mountain bean roots, Sophora flavescens, Sophora alopecuroides, and other leguminous Sophora plants all contain matrine. The pharmacological effects of matrine are numerous and include immunosuppressive, anti-inflammatory, anti-tumour, and cardiovascular protection. For the treatment of viral hepatitis, liver fibrosis, arrhythmia, and autoimmune disorders, among other chronic illnesses, hormone therapy is a popular choice due to its special benefits (40).

Matrine increases the rate of apoptosis in vitro by blocking the growth of FLS, inducing cell cycle arrest in G0/G1 cells, and preventing the activation of the JAK/STAT signalling pathway. By controlling the NF-κB signalling pathway, marine lowers the amount of Th1 cytokines like IFN-γ, tumour necrosis factor (TNF-α), and IL-1β and raises the levels of Th2 cytokines like IL-4 and IL-10 to balance the Th1/Th2 axis (41).

4.3 Terpene alkaloid

4.3.1 Gentianine

Gentianadine, which is the same as synthetic 4-(2′-hydroxyethyl) nicotinic lactone, has been isolated along with gentianine and the three novel alkaloids gentiananine, gentianadine, and gentianamine from Gentianaa turkestanorum and G. olivieri. (42). Gentianine reduced the considerably enhanced production of two pro-inflammatory cytokines (TNF-a and IL-6) by lipopolysaccharide (43).

4.3.2 Aconitine

The tubers of Aconitum plants, which are members of the Ranunculaceae family, are the source of aconitine, a diterpene diester alkaloid. Modern pharmacological research has also verified that aconitine has the following benefits: it reduces pain, reduces inflammation, induces anaesthesia, regulates immunity, lowers blood pressure, inhibits vascular permeability, and has anti-cancer properties (44). Aconitine has demonstrated remarkable effectiveness in reducing inflammation, as seen in the management of rheumatoid arthritis. This is achieved by controlling the levels of cytokines TNF-α and IL-6 and by preventing the NF-κB signalling pathway from being activated (45).

4.4 Purine alkaloid

4.4.1 Theophylline

Theophylline, or 1,3-dimethylxanthine, is a medication that obstructs adenosine receptors and inhibits phosphodiesterase. It is used to treat asthma and chronic obstructive pulmonary disease (COPD). Like other methylxanthine medications (such as theobromine and caffeine), it has a similar pharmacological action. There are naturally occurring trace levels of theophylline in yerba mate, guarana, cocoa, coffee, tea, and kola nuts (46). The proinflammatory transcription factor nuclear factor-κB (NF-κB) is prevented from translocating into the nucleus by theophylline, which may lower the expression of inflammatory genes in COPD and asthma. The prevention of nuclear translocation of activated NF-κB through inhibition of NF-κB appears to be caused by a protective effect against the degradation of the inhibitory protein I-κBα (47).

4.5 Indole alkaloid

4.5.1 Rhynchophylline

One of the tetracyclic oxindole alkaloid is Rhynchophylline (Rhy), which are found in certain species of Uncaria (Gouteng in Chinese, belonging to the family Rubiaceae). It is isolated from *Uncaria rhynchophylla* (Miq.) Jacks U. *tomentosa* and in leaves of *Mitrangya speciose*. This alkaloid has various pharmacological action such as anti-rhythmic, anti-hypertensive, anti-addictive, anticonvulsant, sedative, anti-anxiety, and neuroprotective activities in different experimental models (48). Rhynchophylline (Rhy) suppressed NF-kB, ERK, and p38 MAPKs in N9 microglial cells, hence drastically reducing LPS-induced inflammatory mediators such NO, TNF-α, and IL-1β (49).

4.5.2 Brucine

The seeds of Strychnos nux-vomica L. (Loganiaceae), also known as Nux-vomica (Maqianzi), are used to extract brucine, a weak alkaline indole alkaloid with a bitter flavor and significant toxicity. Brucine has a wide range of pharmacological properties, including anti-inflammatory, anti-tumour, analgesic, and effects on the neurological and cardiovascular systems (50). By triggering the JNK signalling pathway, brucine may prevent the growth of HFLS-RA

cells. The tumour necrosis factor α (TNF-α)-induced proliferation could be greatly reversed and cell viability further inhibited by high dose brucine (> 0.5 mg/ml). Brucine significantly reduces MND %, sponge vascularization, Hb content, CD-31 expression, VEGF, and TGF-b1 in a mouse sponge model. (51)

4.6 Organic amine alkaloid

4.6.1 Colchicine

Colchicine is an organic amino alkaloid which are extracted from the plant known as autumn crocus (Colchicaceae) which are also known as colchicum leuteum baker or *colchicum autumnale* .Colchicine have many pharmacological activity to treat disease like gout, Rheumatism , biliary cirrhosis and cancer(52).Colchicine forms poorly reversible tubulin-colchicine complexes with soluble tubulin, which subsequently attach to the ends of microtubules to stop the microtubule polymer from elongating. Colchicine prevents the release of superoxide, IL1, and IL-8 from neutrophils and their activation (53).

5. GLYCOSIDE

5.1 Ginsenoside

Triterpene saponins and steroid glycosides found in natural products are referred to as ginsenosides or panaxosides. The plant genus Panax contains nearly all of the compounds in this family (ginseng). Ginsenosides can be extracted and purified using column chromatography from different plant sections, however they are usually extracted from the roots. Its many qualities include anti-inflammatory, blood pressure-modulating, antioxidant, anti-apoptotic, and anti-cancer actions(54).Ginsenoside exhibited a substantial inhibitory effect on the expression of cytokines produced from macrophages, including interleukin-1β and tumour necrosis factor-α. Additionally, in activated RAW264.7 macrophages, human synovial cells, and HEK293 cells, G-Rc significantly inhibited the activation of TANK-binding kinase 1/IκB kinase ε/interferon regulatory factor-3 and p38/ATF-2 signalling.(55).

5.2 Paeoniflorin

The main bioactive component of Paeonia suffruticosa Andr., Paeonia lactiflora Pall., or Paeonia veitchii Lynch is pedoniflorin. The pharmacologic actions of paeoniflorin, including immunoregulation, abirritation, hepatoprotection, antihyperglycemic, neuroprotection, cerebrovascular protection, and cardiovascular protection (56). Pae has the ability to inhibit the activation of the NF-κB pathway and reduce TLR4 mRNA or protein expression. Through the suppression of the high mobility group box-1 (HMGB1) -RAGE/ TLR-2/ TLR-4-NF-κB pathway, Pae reduces the generation of inflammatory factors generated by

LPC.Pae reduced the infiltration of CD4+ T cells, CD8+ T cells, and NKT cells in the liver and inhibited the release of proinflammatory cytokines (TNF-α, INF-γ, IL-6) (57).

Conclusion:

Rheumatoid arthritis is one of an auto immune disorder which mostly affects the joints.It is a chronic inflammatory disease which leads to cartilage distruction and bone damage .This may cause due to various reasons like environmental factor , and genetical history etc .There are various types of treatment to reduce the sign of RA but the disease will not be completely cured .The drugs taken for RA has to be consumed for more than 6 months which gives various side effects like gastrointestinal disorder , immunodeficiency and humoral disturbances, cardiovascular complications etc...In such cases , approaching phytoconstituents like alkaloid, flavanoids , polyphenols , glycosides having capabilities of reversing sign of arthritis with minimal side effects.Therefore, finding effective and minimal-toxic active substances from phyto-medicines for treating RA, is an important for developing direction for treatment at present and in the future.so, with more extensive and in-depth research and clinical trials, it is hoped that phytomedicines , including diet and herbs, will be more widely accepted, used alone or as adjuvant drugs for the treatment of RA .

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