Innovative Approaches in Rheumatoid Arthritis: Utilizing Plants to Inhibit TNF-Alpha Production

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent joint inflammation, progressive joint damage, and elevated levels of pro-inflammatory cytokines, especially tumor necrosis factor alpha (TNF-α). While TNF-α inhibitors have revolutionized RA management, challenges such as high cost, adverse effects, and inconsistent patient responses limit their use. These challenges have sparked growing interest in natural plant-based products as potential alternatives or adjuncts for TNF-α inhibition and symptom relief. Numerous medicinal plants traditionally used for their anti-inflammatory properties have demonstrated the ability to reduce TNF-α levels and mitigate RA-related dysfunction. Research into their bioactive compounds reveals antioxidant and immunomodulatory effects targeting multiple inflammatory pathways involved in RA. Preclinical and early clinical studies indicate that these natural agents may offer effective TNF-α suppression and decrease systemic inflammation, with potentially fewer side effects than some synthetic biologics. Combining plant-derived compounds with conventional treatments, within a personalized medicine framework, may enhance therapeutic outcomes for RA patients. However, rigorous systematic studies are necessary to confirm efficacy, understand mechanisms, and ensure safety. Integrating traditional herbal knowledge with modern biomedical research could transform RA treatment, offering safer, more holistic approaches to managing this debilitating condition.

Keywords: TNF-alpha Inhibition; Rheumatoid Arthritis (RA); Plant-Derived Compounds; Curcumin; Anti-inflammatory; Bioavailability; Integrative Therapies

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Introduction

Overview of Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic autoimmune disease causing inflammation and progressive damage to synovial joints, especially in the hands and feet. It results in pain, swelling, stiffness, and can lead to joint deformity and disability. RA is systemic, affecting organs like the skin, eyes, lungs, and cardiovascular system. Although its exact cause is unknown, RA arises from a combination of genetic predisposition and environmental factors that trigger an abnormal immune response, causing the immune system to mistakenly attack the body's own tissues, leading to chronic inflammation and tissue damage (T. Iqbal, Altaf, Salma, et al., 2024).

The Role of Tumor Necrosis Factor-alpha (TNF-alpha) in RA Pathogenesis

Tumor Necrosis Factor-alpha (TNF-α) is a crucial pro-inflammatory cytokine in rheumatoid arthritis (RA) development and progression. Produced mainly by activated synovial fibroblasts and macrophages in inflamed joints, TNF-α triggers a cascade of inflammatory responses. It promotes immune cell recruitment, stimulates other pro-inflammatory cytokines, and increases adhesion molecule expression, driving chronic inflammation and joint damage in RA. Elevated TNF-α levels correlate with RA disease activity and severity in both synovial fluid and systemic circulation. This central role makes TNF-α a primary target for therapeutic interventions aimed at controlling RA symptoms and progression (M. U. Iqbal, Altaf, Naeem, et al., 2024).

Traditional Treatment Approaches Targeting TNF-alpha

Conventional rheumatoid arthritis (RA) treatment has primarily focused on reducing inflammation and managing symptoms to slow disease progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are commonly used to alleviate pain and

inflammation but offer limited protection against joint damage. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, remain the cornerstone of treatment due to their ability to slow RA progression. The advent of biologic therapies, especially TNF-α inhibitors like infliximab, etanercept, and adalimumab, has revolutionized RA management by targeting specific inflammatory pathways, reducing inflammation, and preventing joint destruction. However, biologics are costly and associated with potential adverse effects, including increased infection and cancer risks, highlighting the need to explore additional adjunct therapies to improve treatment outcomes (Umair et al., 2022).

Introduction to the Innovative Use of Plant-Derived Compounds to Inhibit TNF-alpha Production

Due to the limitations and risks associated with conventional TNF-α inhibitors, there is increasing interest in alternative and adjunct treatments for rheumatoid arthritis (RA). One promising area involves bioactive chemicals derived from plants, known as phytochemicals, which have demonstrated the ability to modulate immune responses and inhibit TNF-α production. Medicinal plants have historically provided therapeutic agents, and extensive research spanning 6,000 to 10,000 studies supports the in vivo efficacy of various anti-inflammatory phytochemicals. These natural compounds offer potential advantages, including safer profiles and lower costs compared to synthetic biologics. Additionally, some phytochemicals may exert their effects through biologically relevant mechanisms, targeting cellular signaling pathways involved in inflammation, making them promising candidates for more integrative and sustainable RA treatment strategies (Tasleem et al., 2024).

2. Rheumatoid Arthritis and TNF-Alpha

Pathophysiology of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disorder marked by chronic inflammation of synovial joints, leading to progressive joint damage, persistent pain, and impaired function. It arises from a combination of genetic, environmental, and immunological factors. Individuals with genetic susceptibility may develop inappropriate immune responses triggered by environmental exposures such as infections, cigarette smoke, and hormonal changes. These responses result in the production of autoantibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). These autoantibodies form immune complexes that deposit in the inflamed synovial membrane, activating the complement system and initiating inflammation. The inflamed synovial tissue, or pannus, contains proliferating fibroblast-like synoviocytes, macrophages, T and B lymphocytes, and plasma cells, which create a self-perpetuating proinflammatory environment. Prolonged inflammation leads to cartilage and bone destruction, causing joint deformities and loss of function in affected individuals (T. Iqbal & Altaf, 2024).

The Inflammatory Cascade and the Central Role of TNF-Alpha

Tumor necrosis factor-alpha (TNF-α) is a key cytokine driving rheumatoid arthritis (RA) progression. It is mainly produced by activated macrophages, synovial fibroblasts, and T lymphocytes within affected joints. TNF-α is regarded as the master regulator of inflammation, initiating and amplifying a cascade of proinflammatory molecules and immune responses. It acts through two primary receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), found on various cells including endothelial cells, immune cells, and fibroblasts. Binding of TNF-α to these receptors activates intracellular signaling pathways such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs). This activation upregulates inflammatory molecules like interleukin-1 (IL-1), interleukin-6 (IL-6), chemokines, and matrix metalloproteinases (MMPs), which further promote inflammation, immune cell recruitment, and joint tissue destruction and remodeling (Altaf, Iqbal, et al., 2024).

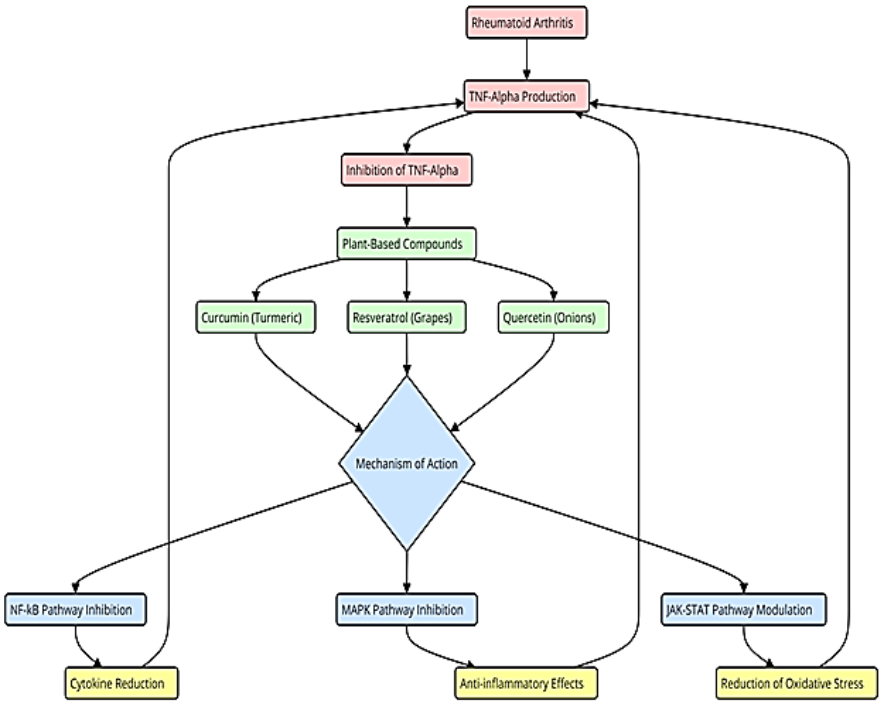

Fig. 1: Plant-based compounds inhibit the production of TNF-Alpha

Mechanisms through which TNF-Alpha Contributes to Joint Inflammation and Destruction

Tumor Necrosis Factor-alpha (TNF-α) plays a central role in rheumatoid arthritis (RA) pathogenesis by driving inflammation and structural joint damage through multiple coordinated pathways. TNF-α increases synovial inflammation by inducing adhesion molecules on endothelial cells, facilitating immune cell recruitment and infiltration into the synovial membrane. The accumulation of inflammatory cells escalates the local immune response. TNF-α also activates synovial fibroblasts and osteoclasts directly. IL-1, induced by TNF-α, stimulates synovial fibroblast proliferation and the release of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs), which cause pannus formation, extracellular matrix degradation, and joint cartilage scarring. Simultaneously, TNF-α promotes osteoclast differentiation and activation, leading to bone erosion. It disrupts immune regulation by suppressing regulatory T cells (Tregs) and promoting pro-inflammatory T helper 17 (Th17) cells, sustaining inflammation. TNF-α also induces angiogenesis in synovial tissue, forming new blood vessels that supply oxygen, nutrients, and immune cells to inflamed joints, perpetuating inflammation and accelerating joint destruction (T. Iqbal, Altaf, Fatima, et al., 2024).

Limitations and Side Effects of Current TNF-Alpha Inhibitors

TNF-α inhibitors such as infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab have revolutionized rheumatoid arthritis (RA) treatment, but their use comes with significant limitations and potential adverse effects. The most prominent limitation is their high cost, which restricts access for many patients, particularly those in low-income settings, and places a heavy financial burden on healthcare systems. Another major concern is the increased risk of infections, as TNF-α plays a critical role in immune defense against pathogens. Inhibiting TNF-α can impair immune function, increasing susceptibility to opportunistic infections like tuberculosis, fungal infections, and various bacterial and viral diseases. Long-term use is also linked to a higher risk of certain cancers, including lymphomas and skin cancers, possibly due to compromised immune surveillance of tumor cells. Additionally, some patients develop anti-drug antibodies that neutralize the biologics, reducing their effectiveness and causing treatment resistance. Other adverse effects include injection site reactions and rare autoimmune complications such as lupus-like syndromes, highlighting the need for careful patient monitoring (T. Iqbal, Altaf, Basit, et al., 2024).

3. Potential of Plant-Derived Compounds in RA Management

Overview of Medicinal Plants Traditionally Used in Inflammatory Conditions

Medicinal plants have played a vital role in traditional medical systems worldwide for generations, particularly in managing inflammatory conditions like arthritis. Curcuma longa (turmeric), widely used in Ayurvedic and Traditional Chinese Medicine, contains curcumin, a powerful anti-inflammatory compound that helps alleviate joint pain and swelling in arthritis patients. Salix alba (white willow bark), traditionally used across Europe and Asia, contains salicin, a natural precursor to aspirin, known for its analgesic and anti-inflammatory properties. Green tea (Camellia sinensis), rich in polyphenols—especially epigallocatechin gallate (EGCG)—offers anti-inflammatory and immunomodulatory effects, showing promise in managing autoimmune diseases like rheumatoid arthritis (Azeez & Lunghar, 2021). Zingiber officinale (ginger), another traditional remedy, contains gingerols and shogaols, compounds with significant anti-inflammatory effects (Bischoff-Kont & Fürst, 2021). Boswellia serrata, or Indian frankincense, provides boswellic acids, which demonstrate anti-inflammatory activity and may help prevent cartilage loss. Incorporating these medicinal plants into RA treatment plans may offer complementary benefits by targeting inflammation through natural bioactive compounds, potentially improving patient outcomes and reducing reliance on synthetic drugs (T. Iqbal, Salma, Umair, et al., 2024).

Bioactive Compounds in Plants That Can Modulate Immune Responses

The therapeutic value of medicinal plants in managing rheumatoid arthritis (RA) primarily stems from their bioactive compounds, which exhibit anti-inflammatory, antioxidant, and immunomodulatory effects. These compounds modulate immune responses, inhibit inflammation, and help prevent joint destruction. Key plant-derived bioactives include curcumin, boswellic acids, gingerols, shogaols, epigallocatechin gallate (EGCG), resveratrol, and quercetin. Curcumin, a polyphenol from turmeric, is well known for its potent antioxidant and anti-inflammatory properties, notably inhibiting NF-κB activation—a transcription factor critical for pro-inflammatory cytokine expression, including TNF-α. Boswellic acids from Boswellia serrata inhibit 5-lipoxygenase, reducing leukotriene production, and suppress pro-inflammatory cytokines like TNF-α and IL-1β, contributing to their anti-inflammatory effects (T. Iqbal et al., 2023). Plant compounds can inhibit TNF-α production by targeting several steps in the inflammatory cascade of RA. A major mechanism involves suppressing NF-κB activation, which reduces transcription of TNF-α and other cytokines. Compounds such as curcumin, EGCG, and resveratrol show promise in downregulating this pathway, potentially offering safer and effective alternatives or adjuncts to conventional therapies (Altaf & Iqbal, 2023). Table 1 presents overview of different plant-based compounds that can be used to inhibit TNF-alpha production in the management of rheumatoid arthritis.

4. Innovative Plant-Based Approaches to Inhibit TNF-Alpha

Curcumin (Turmeric) Anti-inflammatory Effects

Curcumin is a polyphenolic compound from the spice turmeric (Curcuma longa), and has well-established anti-inflammatory and antioxidant properties. Curcumin affects several signaling molecules involved in the inflammatory response. These signaling molecules include cytokines, transcription factors and enzymes. Curcumin is a particularly effective inhibitor of NF-κB, which is a transcription factor that mediates the expression of pro-inflammatory cytokine gene expression (such as TNF-alpha; interleukin-1 beta (IL-1β); and interleukin-6 (IL-6). Curcumin inhibits the activity of NF-κB, leading to reduced pro-inflammatory cytokine secretion and modulation of the inflammatory response. Curcumin has been shown to modulate TNF-alpha levels in a number of studies (including studies from clinical, in vivo models and

animal models of rheumatoid arthritis (RA), whereby curcumin significantly reduces TNF-alpha level in synovial tissue and serum that leads to reduced inflammation and joint destruction (Fatima et al., 2023).

Table 1: Overview of different plant-based compounds that can be used to inhibit TNF-alpha production in the management of rheumatoid arthritis

Sr.No	Source	Plant Compound	Mechanism of Action	Effect on TNF-alpha	Clinical Evidence	Benefits	Challenges	Combination Potential	Future Research Directions	References
1	Turmeric (Curcuma longa)	Curcumin	Inhibits NF-κB activation	Reduces TNF-alpha production	Clinical trials show reduced inflammation in RA	Anti-inflammatory, antioxidant	Low bioavailability	Combines well with DMARDs and NSAIDs	Nano-formulations to enhance bioavailability	(Zeng et al., 2022)
2	Grapes, Berries	Resveratrol	Modulates SIRT1 and NF-κB pathways	Decreases TNF-alpha levels	Limited trials; promising results in RA models	Antioxidant, anti-inflammatory	Variable concentration in natural sources	Synergistic with curcumin for enhanced effects	Focus on optimal dosing and delivery systems	(Pinilla-González et al., 2024)
3	Green Tea (Camellia sinensis)	EGCG	Inhibits NF-κB, JAK/STAT pathways	Suppresses TNF-alpha synthesis	Evidence from inflammatory models; limited in RA	Immunomodulatory, antioxidant	Poor absorption	Potential with methotrexate and biologics	Controlled-release and liposomal formulations	(Bhoi et al., 2024)
4	Boswellia serrata	Boswellic Acids	Inhibits 5-lipoxygenase and NF-κB	Lowers TNF-alpha	Clinical trials show efficacy in reducing RA symptoms	Reduces joint swelling and pain	Standardization issues	Effective with corticosteroids	Explore combination with other phytochemicals	(Roy et al., 2019)
5	Ginger (Zingiber officinale)	Gingerols	Inhibits COX, LOX, TNF-alpha	Reduces pro-inflammatory cytokines	Preliminary human studies; animal model evidence	Anti-inflammatory, analgesic	Inconsistent potency in extracts	Enhances effects of NSAIDs	Further clinical trials on dosing and efficacy	(Chauhan et al., 2022)
6	Onions, Apples	Quercetin	Inhibits MAPK, NF-κB pathways	Reduces TNF-alpha production	Limited clinical data; strong in vitro evidence	Antioxidant, anti-inflammatory	Low bioavailability	Potential with biologics	Nano-formulation to enhance therapeutic effect	(Khare et al., 2020)
7	Garlic (Allium sativum)	Allicin	Modulates immune response, inhibits NF-κB	Reduces TNF-alpha production	Early-stage research; animal studies showing promise	Antimicrobial, anti-inflammatory	Odor, gastrointestinal side effects	Use with standard RA therapies	Formulation research to improve patient compliance	(Kayesth et al., 2024)
8	Ashwagandha (Withania somnifera)	Withanolides	Inhibits pro-inflammatory cytokines, modulates immune cells	Lowers TNF-alpha, IL-1β levels	Preliminary studies suggest potential benefits	Adaptogenic, reduces stress responses	Dosage standardization	Combines with lifestyle interventions	Larger scale clinical trials in diverse population	(Tiwari et al., 2018)
9	Green Tea, Cocoa	Catechins	Antioxidant, anti-inflammatory	Inhibits TNF-alpha production	Limited human trials; promising in animal models	Cardioprotective, anti-inflammatory	Poor solubility in water	Potential with standard RA therapies	Enhanced formulations for better absorption	(Sarkar et al., 2016)
10	Black Pepper (Piper nigrum)	Piperine	Enhances bioavailability of curcumin and other compounds	No direct effect; potentiates other compounds	Studies show increased efficacy of curcumin when combined	Bioavailability enhancer	Gastrointestinal side effects	Used to enhance other plant compounds	Explore effects in combination with multiple phytochemicals	(Srinivasan, 2007)
11	Chili Peppers (Capsicum spp.)	Capsaicin	Inhibits substance P and pro-inflammatory mediators	Reduces local inflammation	Topical formulations reduce joint pain in RA	Analgesic, reduces pain signaling	Skin irritation, burning sensation	Topical use with systemic therapies	Formulation improvements to minimize irritation	(Gupta et al., 2024)
12	Olive Leaf (Olea europaea)	Oleuropein	Antioxidant, anti-inflammatory	Reduces TNF-alpha levels	Preclinical studies show anti-inflammatory potential	Cardioprotective, anti-inflammatory	Variable potency in natural extracts	Combines with heart-healthy diets	Human trials to validate preclinical findings	(Silvestrini, 2022)

13	Scutellaria baicalensis	Baicalin	Inhibits NF-κB, MAPK pathways	Suppresses TNF-alpha production	Preclinical studies suggest anti-inflammatory effects	Neuroprotective, anti-inflammatory	Limited human research	Potential with neuroprotective agents	Further studies on combined neuroprotective effects	(Cowley & Deinert, 2022)
14	Goldenseal (Hydrastis canadensis)	Berberine	Modulates immune response, NF-κB inhibition	Reduces TNF-alpha and other cytokines	In vitro studies show anti-inflammatory effects	Antimicrobial, anti-inflammatory	Gastrointestinal side effects	Combines with gut microbiota modulation	Research into dual anti-inflammatory and antimicrobial effects	(Cecil, 2011)
15	Buckwheat, Citrus Fruits	Rutin	Antioxidant, reduces vascular permeability	Lowers TNF-alpha production	Limited clinical data, mainly animal models	Vascular health, anti-inflammatory	Low bioavailability	Combines with cardiovascular treatments	Explore potential in vascular inflammation in RA	(Ferraz et al., 2020)
16	Parsley, Chamomile	Apigenin	Modulates NF-κB, MAPK, and other pathways	Inhibits TNF-alpha production	In vitro evidence suggests potential effects	Antioxidant, anti-inflammatory	Limited bioavailability	Potential with anti-allergy medications	Investigate combinatorial effects in RA and allergies	(Chirumbolo, 2014)
17	Tomatoes, Watermelon	Lycopene	Antioxidant, modulates inflammatory pathways	Lowers TNF-alpha and oxidative stress	Epidemiological evidence; limited clinical trials	Cardioprotective, anti-inflammatory	Dietary variability affects intake	Effective in combination with heart-healthy diets	Research on dosage standardization in supplements	(Houston, 2016)
18	Microalgae, Salmon	Astaxanthin	Antioxidant, reduces oxidative stress	Lowers TNF-alpha production	Preliminary clinical studies in oxidative stress conditions	Antioxidant, supports eye health	High cost, limited natural sources	Combines with omega-3 fatty acids	Expand clinical trials to inflammatory diseases	(Colletti et al., 2021)
19	Citrus Fruits	Naringenin	Inhibits NF-κB, modulates immune response	Reduces TNF-alpha levels	Early-stage research, animal models	Antioxidant, improves metabolism	Low bioavailability	Potential in metabolic syndrome management	Investigate role in metabolic-inflammatory nexus	(Jiang et al., 2019)
20	Citrus Fruits	Hesperidin	Antioxidant, anti-inflammatory	Lowers TNF-alpha and IL-6	Some evidence in metabolic and inflammatory disorders	Cardioprotective, vascular health	Low bioavailability	Combines with bioflavonoids	Human trials to explore cardiovascular and inflammatory benefits	(Ahmad et al., 2023)
21	Skullcap (Scutellaria baicalensis)	Baicalein	Inhibits pro-inflammatory cytokines	Reduces TNF-alpha production	Preclinical evidence in RA models	Neuroprotective, anti-inflammatory	Limited human data	Combines with other neuroprotective agents	Research on neuro-inflammatory conditions in RA	(Wang et al., 2021)
22	Tea, Nuts, Berries	Tannins	Antioxidant, anti-inflammatory	Reduces TNF-alpha and other cytokines	Limited direct evidence in RA; general anti-inflammatory effects	Antioxidant, supports gut health	Astringency limits oral use	Effective with probiotic and gut health therapies	Further research on gut-immune interactions in RA	(Hussain et al., 2020)
23	Soybeans, Legumes	Genistein	Modulates estrogen receptors, NF-κB inhibition	Reduces TNF-alpha levels	Some clinical evidence in post-menopausal women with RA	Bone health, anti-inflammatory	Potential hormonal effects	Combines with hormone replacement therapies	Explore gender-specific effects in RA management	(Čoma et al., 2021)

Resveratrol (Berries, Grapes) Mechanism of Action as an Anti-inflammatory Agent

Resveratrol is a dietary polyphenol, present in peanuts, berries and grapes, having strong anti-inflammatory, immunomodulatory and antioxidant actions. It blocks NF-κB and activator protein-1 (AP-1) activation, both of which induce transcription of pro-inflammatory genes, such as genes encoding TNF-alpha. Resveratrol also regulates the function of sirtuins, with SIRT1 being identified to inhibit inflammatory cascades and down-regulate TNF-alpha synthesis. In RA animal models, resveratrol administration has been reported to decrease TNF-alpha levels, decrease inflammatory cell infiltration into the synovium, and inhibit bone erosion (Humaira et al., 2023).

Immunomodulatory Impact of Green Tea Polyphenols Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is the primary catechin of green tea (Camellia sinensis) and is best characterized by its strong antioxidant, anti-inflammatory and immunomodulatory properties (Altaf, Iqbal, et al., 2023).

Boswellia Serrata (Frankincense) Anti-inflammatory Activity and TNF-alpha Inhibition

Frankincense, also known as Boswellia serrata, is a resin obtained from the Boswellia tree, and it has a class of active components called boswellic acids. Boswellic acid is a strong anti-inflammatory and analgesic and in studies documented with the International Journal of Phytotherapy research, Boswellic acids inhibits 5-lipoxygenase by blocking the synthesis of leukotrienes (M. Saleem et al., 2024). Boswellic acids also demonstrate the ability to inhibit TNF-alpha synthesis via inhibition of NF-κB and decrease the synthesis of other proinflammatory cytokines. There are several active trials evaluating the effectiveness of Boswellia serrata to patients with rheumatoid arthritis (Saqib et al., 2023). In one randomized clinical that studied Boswellia serrata extract, showed a significant positive effect on reducing joint swelling, and pain, and also reducing TNF-alpha levels on RA patients, compared to a treatment with placebo. In another study, Boswellia was combined with standard conventional RA therapy, which also demonstrated improved clinical outcome and reduced need for corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Promising Plants (Altaf, Khan, et al., 2023).

5. Clinical Evidence and Research Findings

Evaluation of Preclinical and Clinical Investigations of Plant-Wisely TNF-Alpha Inhibitors

As we have seen with studies of herbal TNF-alpha inhibitors for evaluation of rheumatoid arthritis (RA), studies to evaluate the effects of herbal plants can take a long and tortuous path through various preclinical and clinical trials. In these studies, it is important not to mix or confuse herbal plant-based substances with the title of recognizably natural substances that can modulate TNF-alpha; that is, substances that can lower the levels of TNF-alpha (Altaf, Saleem, et al., 2024). TNF-alpha is the most potent inflammatory mediator in RA, and preclinical research has shown significant effects for a number of plant-based substances that exhibit a TNF-alpha inhibitory model. Curcumin in turmeric (Curcuma longa L.) likely decreases the levels of TNF-alpha and inflammation in joint tissues in animal models and it has been shown to inhibit TNF-alpha production in vitro.. Resveratrol, a grape and berry component, lowers TNF-alpha concentrations and inflammatory reactions in RA models. EGCG from green tea polyphenols has inhibited TNF-alpha and anti-inflammatory actions in animal and cell models. Boswellia serrata, or frankincense, lowers TNF-alpha concentrations and inflammation via several mechanisms. Clinical trials, while limited, hold promise (F. Saleem et al., 2023).

6. Benefits and Limitations of Plant-Based Therapies

Advantages of Plant-Based Therapies

Herbal medicine has attracted consideration for rheumatoid arthritis (RA) due to some implied benefits over mainstream drugs. An improvement in side effect risk reduction is one major advantage. While traditional TNF-alpha antagonists have an excessive risk of severe outcomes such as infection, cancers, and autoimmune responses, naturally occurring plant extracts generally possess an improved safety margin (Mushtaq et al., 2024). Agents like curcumin, resveratrol, EGCG, and boswellic acids are well tolerated with less pronounced side effects. Most plant chemicals are accessible as nutritional supplements, herbal extracts, or in naturally occurring forms like turmeric powder or green tea. Due to their widespread availability, patients are able to easily include these therapies in their day-to-day lives without the necessity for specialized scripts or repeated visits to doctors. Furthermore, medicinal plants are traditionally used in most cultures as part of traditional medicine, hence are more acceptable culturally and easier to assimilate into lifestyle habits compared to traditional pharmacological interventions (Salma et al., 2023).

Limitations of Using Plant-Based Therapies

Herbal treatments have some benefits in the management of rheumatoid arthritis (RA), yet they also have challenges that need to be addressed to make them effective and safe. One challenge is the difference in concentrations of plant compounds. The efficacy of active compounds in medicinal plants can vary widely depending on factors such as plant species, growth conditions, when the plant was harvested, and preparation. Although variability in the efficacy and therapeutic effects may introduce inconsistency and unpredictability in patient responses, there are quality control issues as well because there are no standardized cultivation and extraction protocols (Altaf & Iqbal, 2024). For this reason, herbal formulations may contain marginally different amounts of active ingredients, toxins, or even additives that affect its safety and efficacy. Bioavailability is also a consideration when discussing herbal treatment. Many plant-derived compounds ranging from curcumin to resveratrol have low bioavailability, which refers to the limit poor absorption, wide variability in their metabolism and rapid disposition from the body. Low bioavailability may limit therapeutic effectiveness and lead to higher dosing requirements or separate, more complex formulations to achieve therapeutic concentrations. New delivery systems such as nanoparticles, liposomes, and phospholipid complexes are being developed to address bioavailability issues; however, this would require research and increased cost and complexity of care.(Kciuk et al., 2024).

The Need for More Rigorous Clinical Trials and Safety Assessments

There is potential for herbal medications in the treatment of rheumatoid arthritis (RA); however, the evidence supporting their use is currently lacking in the form of proper clinical research, as well as safety studies. There is clearly the need for large dose randomized controlled trials (RCTs). High quality, large multi-center RCTs are required to provide the best evidence for the efficacy, safety and appropriate dosing of RA herbal therapies. One informed design would explore both the single use of these compounds, combined with other herbal medications, or in conjunction with conventional RA treatments, to find the best therapeutic approaches. There is also a need for long-term safety studies. In

addition to obtaining evidence for therapeutic use, long-term studies are critical to understanding the risks that may be associated with long-term use of herbal treatments, particularly in vulnerable populations like the elderly, pregnant women, and people with multiple comorbidities. Knowing the risk of these therapies in the long-term will help to minimize risk and guide clinical practice. Another area for exploration is standardization and quality control. Standardization in growing, extracting, and preparing herbals for therapies is necessary for efficacy, quality, and safety to be consistent. The creation of standardized quality control methods can alleviate dynamic changes and potential contamination while improving the consistency and certainty of the therapy's use (Y. Wang et al., 2021). Finally, pharmacokinetic and pharmacodynamic studies can facilitate the better recognition of plant-based agents. Pharmacokinetics refers to the absorption, distribution, metabolism, and excretion of plant agents and their properties. Pharmacodynamics identifies biological effects and mechanisms of action of these plant agents, which is useful in the development of therapies aimed at optimizing their effectiveness (Gulnaz et al., 2023).

7. Future Areas of Research and Emerging Developments in Plant-based Therapeutics for RA

Emerging developments in herbal treatment of RA (rheumatoid arthritis) demonstrate an evolving approach to herbal therapies that includes new bioactive molecular compounds, new drug delivery devices or methods, integrative medicine, and personalized medicine practices. Several researchers have unearthed new and innovative plant-based (phytotherapeutic) molecular compounds that have an anti-inflammatory action in RA, even synthesizing analogs that could improve efficacy and bioavailability for those cases that are found to be unsuccessful with the herbal therapies starting material. New drug delivery technologies are also developing (e.g., nanotechnology, controlled release systems) that may offer an advantage over conventional systems (T. Iqbal et al., 2024).

The potential for exploring combinations of several different plant-derived chemicals that could yield synergistic anti-inflammatory activity and improve disease control should not be overlooked. These developments illustrate an encouraging future for domestic herbal remedies to be integrated into holistic patient-centred models of care for rheumatoid arthritis (Faisal et al., 2024).

Conclusion

Plant-derived molecules targeting TNF-α offer a promising alternative or complementary approach for rheumatoid arthritis (RA) treatment. These compounds have demonstrated anti-inflammatory effects with fewer adverse reactions and lower costs compared to conventional TNF-α inhibitors. Herbal therapies could transform RA management by providing safer, more affordable options that improve patients' overall health and quality of life. However, further research is essential to fully understand their efficacy, safety, and optimal use. Large-scale clinical trials are needed to validate their therapeutic potential. Additionally, advanced formulation techniques and personalized medicine approaches will be crucial to successfully integrate these natural compounds into standard RA care. Combining traditional botanical wisdom with modern scientific advancements could usher in a new era of RA treatment, offering patients effective, natural therapies that support holistic health. This synergy of nature and science holds great promise for enhancing RA management and patient outcomes.

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