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Review Article

Role of Extraction Process of Herbal Medicine in Anti-Inflammatory Diseases

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ABSTRACT

Inflammatory diseases, characterized by acute or chronic immune responses, play a significant role in the pathogenesis of conditions such as arthritis, inflammatory bowel disease (IBD), and cardiovascular diseases. Conventional treatments, including nonsteroidal anti-inflammatory drugs and corticosteroids, often present limitations related to side effects and long-term safety. Herbal medicine, rich in bioactive compounds like flavonoids, terpenoids, and alkaloids, offers a promising complementary approach to managing inflammation. The efficacy of herbal therapies largely depends on extraction processes that isolate and preserve these active constituents. Various extraction techniques, including solvent extraction (using ethanol, methanol, water), supercritical fluid extraction (SFE), cold press, steam distillation, ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and enzyme-assisted extraction, influence the yield, potency, and bioavailability of anti-inflammatory compounds. Solvent polarity and extraction methods significantly affect the composition and biological activity of herbal extracts. Moreover, the pharmacokinetics and bioavailability of these compounds determine their therapeutic potential in vivo. Clinical studies have demonstrated the efficacy of herbal extracts such as turmeric, Boswellia, and ginger in reducing inflammation with favorable safety profiles. However, toxicity concerns and herb-drug interactions necessitate rigorous safety evaluations. Regulatory frameworks vary globally, underscoring the need for standardization and quality control. Future research should focus on innovative, green extraction technologies, clinical validation, and integration of traditional knowledge with modern medicine. Personalized herbal medicine tailored to individual inflammatory profiles holds potential for enhanced treatment outcomes. This review highlights the critical role of extraction processes in maximizing the anti-inflammatory potential of herbal medicines, addressing safety, efficacy, and future directions in inflammatory disease management.

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INTRODUCTION

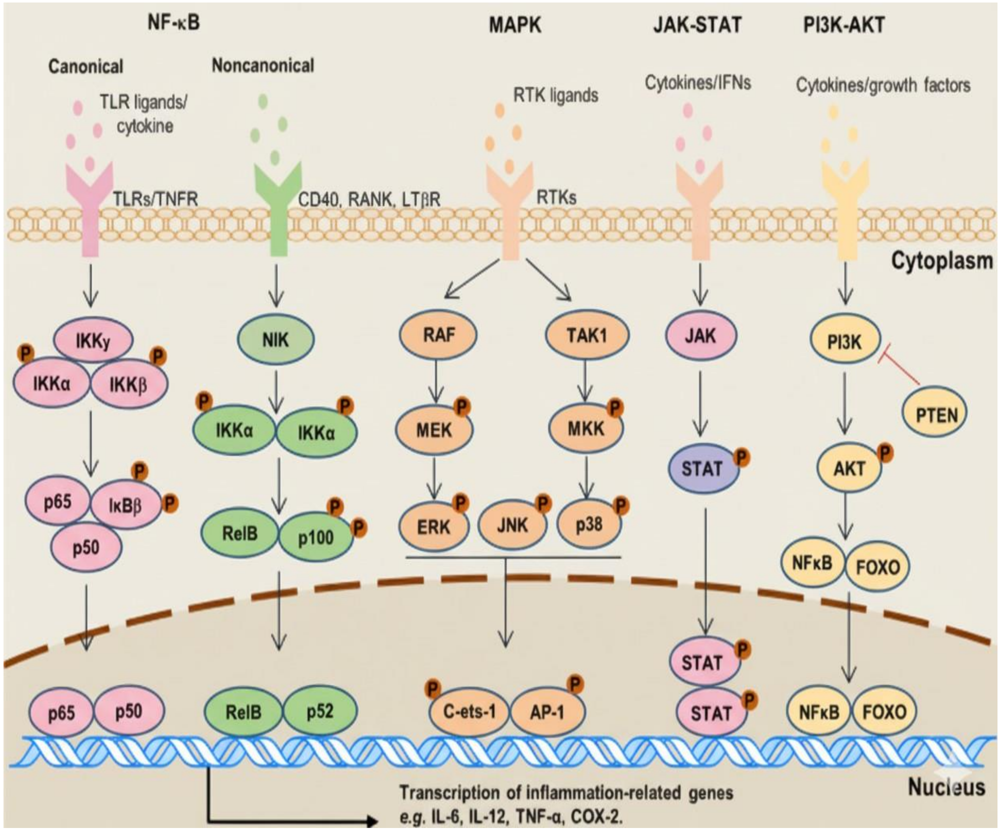
Inflammation is a fundamental biological response that acts as the body's initial defence mechanism against harmful stimuli such as pathogens, damaged cells, and irritants. While acute inflammation is vital for tissue repair and the resolution of injury, prolonged or dysregulated inflammation—commonly referred to as chronic inflammation—has been implicated in the pathogenesis of numerous diseases, including cancer, cardiovascular disorders, and autoimmune conditions [1]. Inflammatory disease refers to a broad category of medical diseases that impact numerous organs and tissues. Atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma, psoriasis, and inflammatory bowel disease are examples of inflammatory disorders. Asthma and other atopic illnesses have become much more common in recent decades. Crohn's disease, which is more severe but less common, and ulcerative colitis were both thought to be diseases of Western society, although they are becoming more common and occurrence throughout Asia. People with inflammatory bowel illness have a higher chance of acquiring colorectal cancer. In areas with diets rich in n-3 polyunsaturated fatty acids (PUFAs), the prevalence of cancer is low. There have been suggestions that dietary n-3 PUFAs' anti-inflammatory and PPAR-activating qualities may contribute to some of their beneficial effects [2]. Herbal medicines are gaining significant attention in healthcare, highlighting the need to deepen our understanding of their properties. While complementary, alternative, and traditional medicine provide valuable insights into herbal treatments, it is essential that modern medical research rigorously validates these claims through scientific studies before clinical application. This review aims to evaluate various plants and the strongest clinical evidence supporting their anti-inflammatory benefits [3]. Active chemicals from medicinal plants have been extracted and characterized, leading to the discovery of novel medications with significant therapeutic benefits. Farnsworth et al. discovered 119 secondary plant metabolites that were utilized as medications in 1985. Eleven percent of the 255 medications that the World Health Organization (WHO) considers basic and essential come from plants, and several synthetic medications are also derived from natural precursors. Phytochemicals are widely employed in medicine because of their known antioxidant, antibacterial, antifungal, antidiabetic, anti-inflammatory, antiarthritic, and radio-protective activity qualities [4].

INFLAMMATORY PATHWAY AND THEIR MEDIATORS

Inflammation is a complex biological response triggered by harmful stimuli such as pathogens, damaged cells, or irritants. It serves as a protective mechanism aimed at removing the initial cause of injury, clearing out dead cells, and initiating tissue repair. The inflammatory pathway involves a series of coordinated events regulated by various signaling molecules known as inflammatory mediators. These mediators, including cytokines, chemokines, prostaglandins, and histamine, play critical roles in modulating vascular changes, recruiting immune cells, and amplifying the immune key response [5]. Understanding these pathways and the mediators involved is essential for deciphering the mechanisms of many diseases and developing targeted therapeutic strategies.

Inflammatory pathway include:

- NF- kB pathway
- MAPK pathway
- JAK-STAT pathway [6]



ROLE OF CHRONIC INFLAMMATION IN DISEASE

Chronic inflammation is a prolonged immune response that can persist for months or even years, depending on the underlying cause and the body's healing capacity. It may develop when the body fails to eliminate harmful agents like certain bacteria, fungi, or parasites, or due to long-term exposure to non-degradable irritants such as industrial dust. Autoimmune conditions, where the immune system mistakenly targets healthy tissues, and genetic disorders affecting inflammatory responses can also lead to chronic inflammation. Additionally, it can result from repeated acute inflammation or arise independently due to factors like oxidative stress and the buildup of damaging molecules such as free radicals and uric acid. Chronic inflammatory diseases are a leading cause of death globally and pose a significant threat to public health. The World Health Organization identifies chronic conditions as the most serious challenge to human health, with their prevalence expected to rise steadily over the next few decades. In the United States alone, about 125 million people had chronic conditions by 2000, and by 2014, around 60% had at least one chronic illness, with 42% having multiple conditions. Worldwide, three out of five deaths are linked to chronic inflammation-related diseases such as heart disease, stroke, diabetes, obesity, cancer, and respiratory illnesses.

- **Diabetes:**
  In 2015, 30.3 million Americans (9.4% of the population) had diabetes, making it the 7th leading cause of death in the U.S.

- **Cardiovascular Diseases (CVD):**
  CVD causes about 1 in every 3 deaths in the U.S. (~800,000 deaths yearly). Globally, it accounts for 31% of all deaths, with coronary heart disease as the leading cause, followed by stroke and heart failure.

- **Arthritis and Joint Diseases:** These affect approximately 350 million people worldwide and nearly 43 million Americans (around 20% of the population). This is expected to rise above 60 million by 2020. About 2.1 million Americans have rheumatoid arthritis.

- **Allergies:** Allergies rank as the sixth leading cause of chronic diseases in the U.S., affecting over 50 million people annually. Asthma impacts more than 24 million Americans, including over 6 million children. In 2015, about 8.2% of adults and 8.4% of children had hay fever.

- **Chronic Obstructive Pulmonary Disease (COPD):** COPD was the third leading cause of death in the U.S. in 2014, with nearly 15.7 million Americans (6.4%) diagnosed with the condition [7].

INNOVATIVE APPROACHES TO INFLAMMATORY DISEASE MANAGEMENT

Plant Name	Active Compounds	Traditional Uses	Modern Application	Anti-Inflammatory Mechanism
Turmeric (Curcuma longa)	Curcumin	Treating wounds, digestive issues, and inflammation	Arthritis, IBD, neuroinflammation	Block NF-kB and COX-2 signalling Pathways, reducing inflammation
Ginger (Zingiber officinale)	Gingerols	Nausea, colds, arthritis	Osteoarthritis, RA, muscle pain	Lowers prostaglandin and leukotriene synthesis, reducing pain and swelling
Willow Bark (Salix alba)	Salicin	Fever, pain, inflammation	Natural aspirin alternative for joint pain	Inhibits cyclooxygenase (COX) enzymes, cutting prostaglandin production
Boswellia (Boswellia serrata)	Boswellic acids	Joint pain, swelling, asthma	Osteoarthritis, ulcerative colitis, asthma therapy	Suppresses 5- LOX enzyme, lowering leukotriene production
Green Tea (Camellia sinensis)	Epigallocatechin gallate	General health, mental alertness	Autoimmune diseases, metabolic syndrome	Down regulate inflammatory cytokines and oxidative stress
Licorice (Glycyrrhiza glabra)	Glyrrhizin	Cough, stomach ulcers, adrenal support	Inflammatory bowel disease, eczema	Balance cortisol activity and inhibit TNF-a
Neem (Azadirachta indica)	Nimbin, Azadirachtin	Skin disorders, fever, infections	Psoriasis, eczema, arthritis	Suppresses cytokines and reduces inflammatory mediator activity
Ashwagandha (Withania somnifera)	Withanolige	Stress, fatigue, immune boosting	Neuroinflammation, autoimmune disorders	Lower C-reactive protein (CRP) AND modulates immune response
Cat’s Claw (Uncaria tomentosa)	Oxindole alkaloid	Arthritis, infections, digestive disorders	Rheumatoid arthritis, IBD	Inhibit TNF-a and NF-kB signalling, reducing chronic inflammation

Devil's Claw (Harpagophytum procumbens)	Harpagoside	Joint pain, fever, inflammation	Back pain, osteoarthritis, muscle inflammation	Inhibits COX-2 and nitric oxide production, easing pain and swelling

HERBAL MEDICINE CONSTITUENTS

Medicinal plants include phytochemicals that can be used to treat various health conditions and serve as a possible source for novel drug development. Phytochemicals and their compounds provide significant clinical benefits, including anti-inflammatory properties. Many plant-derived compounds, including extracts, are being researched for their potential use in the treatment of inflammatory diseases. Polyphenols, terpenoids, flavonoids, saponins, and tannins are the primary phytochemicals responsible for anti-inflammatory properties. Phytochemicals can reduce inflammation stress by increasing the release of systemic mediators, cytokines, and chemokines, leading to cellular infiltration and resolution of inflammatory responses. This promotes tissue coordination. The anti-inflammatory activity mechanism is active at both the cellular and molecular levels. Phytochemicals reduce prostanoids and leukotrienes by inhibiting regulatory enzymes like lipoxygenases, cyclooxygenases, phospholipaseA2, histamine generation, protein kinases, phosphodiesterase, and transcriptase activation. In vitro studies have shown that flavonoids, polyphenols, alkaloids, saponins, tannins, and terpenes can reduce inflammation. Quercetin inhibits enzymes that produce ecosanoids from arachidonic acid, including COX-2 and 5-LOX. Resveratrol regulates inflammation by limiting the production of pro-inflammatory mediators, altering eicosanoid synthesis, and suppressing activated immune cells. Flavonoids, curcumins, and tannins have been shown to reduce inflammation by scavenging free radicals and inhibiting proinflammatory enzymes. Although the mode of action of M/MONPs against illnesses is not fully known, several reported data suggest potential mechanisms. Scholars presented many viewpoints to explain the potential mechanisms of action of M/MONPs. According to some literature, M/MONPs bind to phosphorus and sulfur-containing cell components such as DNA and proteins, which eventually breakdown. Natural compounds are utilized to prevent protein denaturation.[8]

ROLE OF ACTIVE COMPOUNDS IN MODULATING INFLAMMATION

Phenolic compounds are secondary metabolites with antioxidative characteristics that are thought to reduce inflammation. Plant-derived products should be prioritized in preventing low-grade chronic inflammation because to their emergency role and antioxidative benefits. This review examines how isolated plant-derived chemicals affect molecular pathways that influence inflammatory responses [9]. Luteolin and LUT-7G have been shown to activate the inflammatory pathway and help resolve inflammation. PRRs, found on antigen-presenting cells like dendritic cells and macrophages, identify microbial agents and endogenous pieces from injured tissues. There are several types of pattern-recognition receptors, including TLRs, NLRs, CLRs, RLRs, CDSs, and FPRs. Toxic compounds, high glucose and fatty acid levels in blood, alcohol, and metals (fluoride, nickel) can activate immune cells and secrete pro-inflammatory cytokines, chemokines, and eicosanoids (e.g., leukotrienes, prostaglandins). Binding PRR receptors to pathogen-associated molecular patterns (PAMPs) results in the generation of three major mediators of acute and chronic inflammation: IL-1β, IL-6, and TNF-α. Luteolin and LUT-7G can prevent the interaction of PAMPs with PRRs and reduce downstream activation signals [10]. Macrophages are involved in all stages of inflammation, including initiation, maintenance, and resolution, as well as antigen presentation, phagocytosis, and immune regulation. Furthermore, macrophages aid in the restoration of tissue function and homeostasis. Macrophages play both beneficial and negative roles in regulating inflammatory responses. However, prolonged inflammation can cause tissue damage and illnesses. Related ailments include diabetes, cardiovascular diseases, chronic respiratory diseases, arthritis, cancer, and obesity. Chronic inflammation is a leading cause of death worldwide. A study on a mouse model of endotoxemia found that the PI3K/AKT pathway inhibits LPS-induced inflammation. Another study found that AKT2 deletion mice exhibited greater resistance to LPS-induced inflammation and dextran sulfate-sodium-induced colitis. AKT1 deletion mice exhibit increased susceptibility to developing pulmonary fibrosis [11]. In general, natural products are thought to be safer than synthetic pharmaceuticals and have been used for centuries to treat a variety of illnesses (Jamshidi-Kia et al., 2018; Nasri and Shirzad, 2013). Many inflammatory diseases have been treated with medicinal plants and the chemicals that make them up. There are several chemical components obtained from plants that have been shown to have anti-inflammatory qualities, including alkaloids, tannins, flavonoids, terpenoids, glycosides, carotenoids, and saponins. The bioactive principles of some significant medicinal plants that are employed as anti-inflammatory medicines have been covered here Curcumin, a bioactive compound from Curcuma longa rhizomes, has long been used as a spice and possesses significant anti-inflammatory and therapeutic potential against diseases like cancer, cardiovascular disorders, Parkinson's, diabetes, and hepatitis. Its anti-inflammatory effects are primarily due to suppression of NF-kB-mediated cytokines (IL-1β, TNF-α), inhibition of enzymes like COX, LOX, and MMP-9, and modulation of dendritic cells reducing immune activation. Studies demonstrate curcumins efficacy in reducing inflammation in models of rheumatoid arthritis, osteoarthritis, colitis, and orbital pseudotumors, often comparable to standard drugs. It also promotes apoptosis in cancer cells via mitochondrial and receptor pathways and shows promise in breast cancer treatment by downregulating Mcl-1. Enhanced formulations like nanogels improve curcumin's anti-inflammatory effects, making it a potent candidate for managing various inflammatory and proliferative disorders. Ginger (Zingiber officinale) is renowned for its anti-inflammatory properties and has been traditionally used to treat arthritis, digestive issues, cardiovascular diseases, diabetes, and cancer. Key active compounds such as 6-gingerol, 6-shogaol, and galanolactone exhibit anti-inflammatory effects by reducing pro-inflammatory cytokines (TNF-α, IL-1, IL-6), nitric oxide, and enzymes like caspase-3, while boosting antioxidant enzymes (SOD, CAT, GST). Ginger extracts and essential oils have shown efficacy in various in vitro and in vivo models, including arthritis, gout, plantar fasciitis, and diabetes, by inhibiting immune cell activation, stabilizing membranes, and modulating inflammatory mediators. Clinical and preclinical studies highlight ginger's potential to reduce inflammation, pain, and oxidative stress, often through modulation of key molecular pathways and receptors, suggesting its promise as a natural anti-inflammatory and anti-arthritic agent with fewer side effects than conventional drugs [12].

HERBAL EXTRACTION TECHNIQUES

The preparation of medicinal plants is a crucial first stage in experimental studies, as it directly influences the reliability of research outcomes. This process typically includes the extraction of plant materials and the evaluation of both the quality and concentration of bioactive compounds, which must be established before moving forward with biological or pharmacological investigations. In plant extraction, the solvent employed is referred to as the menstruum. The selection of a suitable solvent is influenced by factors such as the plant species, the specific part of the plant being processed, the chemical nature of the active constituents, and solvent availability. Typically, polar solvents like water, ethanol, and methanol are preferred for isolating polar compounds, while non-polar solvents such as hexane and dichloromethane are more effective for extracting non-polar constituents.

A. Water

Water is the most polar solvent and is commonly applied in extracting a wide variety of polar constituents.

•Advantages: It can dissolve many different compounds, is inexpensive, non-toxic, non-flammable, and strongly polar.

•Disadvantages: Its use may encourage microbial growth (bacteria and molds), can lead to hydrolysis of certain compounds, and requires high energy input for concentrating extracts due to the large amount of heat needed.

B. Alcohol

Alcohols, being polar and completely miscible with water, are effective in extracting polar secondary metabolites.

• Advantages: At concentrations above 20%, alcohol acts as a preservative; it is safe at low levels, and extract concentration requires relatively little heat.

• Disadvantages: It is unable to dissolve fats, gums, and waxes, and because of its volatility, it is both flammable and unstable at higher temperatures.

C. Chloroform

Chloroform is a non-polar solvent widely used for extracting terpenoids, flavonoids, oils, and fats.

•Advantages: It is colourless, has a sweet odour, dissolves readily in alcohol, and is efficiently absorbed and metabolized by the body.

•Disadvantages: Its major drawbacks are its sedative effects and carcinogenic potential.

D. Ether

Ether, also a non-polar solvent, is suitable for extracting alkaloids, terpenoids, coumarins, and fatty acids.

• Advantages: It mixes easily with water, has a low boiling point, is tasteless, and remains chemically stable without reacting with acids, bases, or metals.

• Disadvantages: Its high volatility and flammability pose significant safety concerns.

E. Ionic Liquids (Green Solvents)

Ionic liquids are unique extraction solvents, highly polar and extremely heat-resistant, capable of remaining liquid at temperatures up to about 3,000 °C. They show excellent miscibility with both water and organic solvents, making them highly effective for extracting polar compounds.

•Advantages: They efficiently absorb and transmit microwaves, making them suitable for microwave-assisted extraction. In addition, they are non-flammable and useful in liquid–liquid extraction processes.

•Disadvantage: Their application is limited in the preparation of tinctures [13].

COMMON EXTRACTION TECHNIQUES

• MACERATION

In this method, the crude drug, either whole or coarsely powdered, is immersed in a suitable solvent inside a closed container and left to stand at room temperature for a minimum of three days with regular shaking to facilitate dissolution of the soluble constituents. After this period, the liquid portion is separated by straining, while the remaining solid residue (marc) is pressed to recover any absorbed liquid. The combined extracts are then clarified either by filtration or by decantation after allowing them to settle.

• PERCOLATION

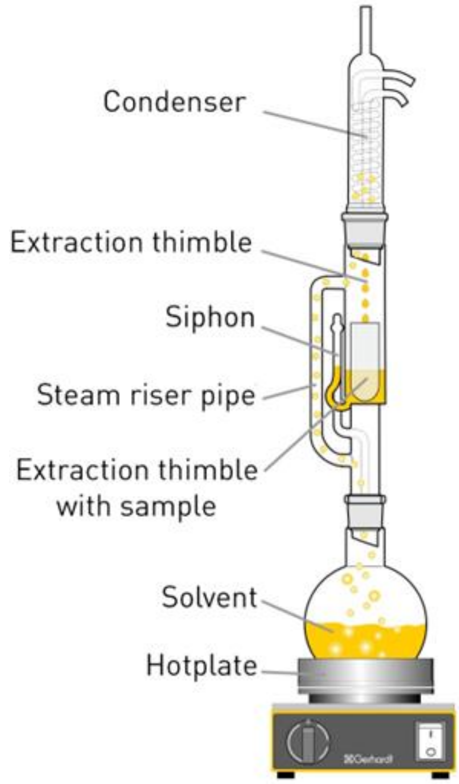
This method, commonly employed for preparing tinctures and fluid extracts, makes use of a percolator, a narrow cone-shaped vessel open at both ends. The powdered drug is first moistened with a suitable quantity of menstruum and left in a closed container for about four hours, after which the material is tightly packed into the percolator and the top is sealed. A small layer of menstruum is added above the drug mass, and the setup is allowed to macerate for 24 hours in the closed vessel. The lower outlet is then opened to allow the liquid extract to drip slowly, while more menstruum is continuously added until nearly three-quarters of the final product volume is collected. The remaining marc is pressed to recover any absorbed liquid, which is combined with the percolate, and additional menstruum is added to reach the desired volume. The final extract is clarified either by filtration or by allowing it to stand and then decanting.

• DECOCTION

In this method, the crude drug is boiled with a specified quantity of water for a set period, after which the mixture is cooled and filtered. It is mainly used for extracting water-soluble and heat-stable compounds. This technique is traditionally employed in Ayurveda for preparing decoctions known as quath or kawath. Generally, the drug-to-water ratio is predetermined, such as 1:4 or 1:16, and the volume is reduced to one-fourth of the initial volume by boiling. The concentrated extract obtained is then filtered and either used directly or subjected to further processing [14].

• SOXHLET EXTRACTION

In this technique, the powdered crude drug is packed into a porous thimble, usually made of strong filter paper, and placed inside the extraction chamber of a Soxhlet apparatus. The solvent kept in the boiling flask is heated, and its vapours condense in the condenser, allowing the condensed liquid to drip onto the drug material. As the chamber fills, the solvent containing the dissolved constituents siphons back into the boiling flask, and the cycle continues repeatedly until the extract is completely obtained, indicated by the absence of residue when a drop of siphoned solvent is evaporated. This continuous process enables efficient extraction of large quantities of drug material using relatively small amounts of solvent, making it highly economical in terms of solvent consumption, time, and energy. While it is commonly applied as a batch process at a laboratory scale, it becomes more practical and cost-effective when adapted for continuous operation in medium- or large-scale production.



• SUPERCRITICAL FLUID EXTRACTION

Supercritical fluid extraction (SFE) is a separation method that uses supercritical fluids (SFs) as solvents, combining the solubility of liquids with the diffusivity of gases, which enables efficient dissolution of various natural products. Their solvent properties can be precisely tuned by small changes in temperature and pressure near the critical point, making the process highly versatile. Supercritical carbon dioxide (S-CO_2) is the most widely used SF due to its low critical temperature (31 °C), inertness, non-toxicity, affordability, and ability to extract heat-sensitive compounds. Its non-polar nature makes it ideal for recovering lipids, essential oils, and other non-polar constituents, while the addition of modifiers such as ethanol can enhance its solvating power for moderately polar compounds. Beyond efficiency, SFE with S-CO_2 is considered environmentally friendly since it leaves no toxic solvent residues and allows easy removal of CO_2 by depressurization, producing safe and high-purity extracts suitable for food, pharmaceutical, and cosmetic applications [15].

• ULTRASONIC -ASSISTED EXTRACTION

Ultrasonic-assisted extraction (UAE), often referred to as sonication, is an advanced technique that uses high-frequency ultrasonic waves to improve the recovery of bioactive compounds from plant and other natural materials. The process relies on acoustic cavitation, where the rapid formation and collapse of microbubbles in the solvent create localized zones of high pressure and temperature, enhancing solvent penetration, solute diffusion, and mass transfer. This not only increases extraction efficiency but also lowers solvent use, reduces energy consumption, and shortens the extraction time. Since UAE can be performed at relatively low temperatures, it is particularly well-suited for isolating thermolabile and sensitive molecules. The method has been widely applied to obtain diverse natural products such as phenolics, flavonoids, polysaccharides, alkaloids, and volatile oils. Beyond its efficiency, UAE is considered a green technology because it minimizes the need for toxic solvents and can be integrated with other sustainable extraction approaches. Its scalability and cost-effectiveness further make it an attractive option for food, pharmaceutical, and cosmetic industries where maintaining the stability and quality of bioactive compounds is essential [13].

COMPARATIVE EVALUATION OF EXTRACTION PROCESSES IN HERBAL ANTI-INFLAMMATORY RESEARCH

Ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) have emerged as advanced extraction methods that often demonstrate superior performance compared to conventional techniques such as maceration and Soxhlet extraction. Both UAE and MAE enhance cell wall disruption, facilitating the release of intracellular metabolites. UAE relies on acoustic cavitation, which generates localized high pressure and temperature, leading to improved solvent penetration and mass transfer. MAE, on the other hand, utilizes electromagnetic waves that heat polar solvents and plant matrices rapidly, reducing extraction time and solvent consumption while improving yield. Studies consistently report that UAE and MAE extracts contain significantly higher concentrations of phenolic compounds, flavonoids, and terpenoids compared to Soxhlet or maceration. Because antioxidant activity is closely linked to the total phenolic and flavonoid content, the higher recovery of bioactive compounds in UAE/MAE translates into stronger radical scavenging capacity. Comparative studies have shown that UAE extracts often display higher DPPH and ABTS radical scavenging activities than maceration, while MAE extracts demonstrate enhanced ferric reducing antioxidant power (FRAP) and oxygen radical absorbance capacity (ORAC) compared to Soxhlet-derived extracts. The enhanced extraction efficiency of UAE and MAE also reflects in stronger anti-inflammatory properties. For example, propolis extracts obtained via UAE and MAE exhibited comparable or superior inhibition of 5-lipoxygenase and nitric oxide production compared to Soxhlet extracts. Similarly, MAE-derived extracts of *Oroxylum indicum* leaves demonstrated increased COX-2 inhibition and cytokine suppression compared to conventional methods. UAE has also been shown to yield extracts with improved cytokine inhibitory responses in *Psoralea coryfolia*, suggesting superior modulation of inflammatory mediators compared to maceration or reflux extraction. While Soxhlet ensures exhaustive extraction, its prolonged heating often degrades heat-sensitive bioactives, limiting anti-inflammatory efficacy. Maceration is milder but less efficient, typically producing lower yields and weaker bioactivity. In contrast, UAE and MAE combine efficiency with compound preservation, thereby generating extracts with higher antioxidant capacity and stronger anti-inflammatory effects, both in vitro and in vivo [16].

SUPERCRITICAL FLUID EXTRACTION EXTRACTS SHOWING UNIQUE TERPENOID PROFILES EFFECTIVE IN ANIMAL MODELS OF INFLAMMATION.

Supercritical fluid extraction (SFE), especially CO_2-based SFE, reliably produces terpenoid-rich extracts that show meaningful anti-inflammatory effects in animal models. SFE concentrates volatile and lipophilic constituents (e.g., turmerones from *Curcuma longa*, isoegomaketone and other terpenoid derivatives from *Perilla frutescens*, ligustilide/gingerol-containing fractions from *Angelica*/*Zingiber* blends) that modulate inflammatory pathways — reducing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), downregulating iNOS/COX-2, limiting oxidative stress, and improving histopathology. These bioactivities have been demonstrated in several in vivo models: TNBS-induced colitis (rats) with improved colon pathology and lowered cytokines, collagen-induced or antibody-induced arthritis (mice) with reduced paw swelling and histologic damage, and topical/ear-edema models showing suppressed edema formation. The potency of SFE extracts reflects both the specific terpenoid profile imparted by supercritical CO_2 conditions and the ability of lipophilic terpenoids to reach inflammatory targets in vivo, although extraction parameters (pressure, temperature, co-solvent) strongly influence yield and composition [17].

EXTRACT COMPOSITION VS. IN VIVO AND IN VITRO ANTI-INFLAMMATORY ACTIVITY

The biological activity of herbal extracts is directly influenced by their phytochemical composition, which is largely determined by the extraction technique employed. Advanced methods such as UAE, MAE, and SFE enhance the recovery of phenolics, flavonoids, and terpenoids, compounds strongly associated with antioxidant and anti-inflammatory potential.

In vitro studies have consistently demonstrated that extracts enriched in polyphenols and terpenoids show potent inhibition of inflammatory mediators. For instance, UAE and MAE extracts from various medicinal plants exhibited stronger suppression of cyclooxygenase-2 (COX-2) activity, reduced nitric oxide (NO) production, and downregulated pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in cell-based assays compared to maceration or Soxhlet extracts. These effects directly correlate with higher phytochemical yields achieved by modern extraction technologies. In vivo evidence further supports these findings. Supercritical fluid extracts (SFE) rich in terpenoids, such as those from *Angelica sinensis* and *Zingiber officinale*, significantly ameliorated inflammation in TNBS-induced colitis rat models by reducing oxidative stress and cytokine levels (Liu et al., 2019). Similarly, UAE- and MAE-derived extracts from herbs like *Curcuma longa* and *Perilla frutescens* showed superior efficacy in animal models, including carrageenan-induced paw edema and arthritis models, compared to conventional extracts. Together, these in vitro and in vivo studies highlight that extraction-driven differences in phytochemical composition are directly linked to the degree of anti-inflammatory activity, emphasizing the importance of optimizing extraction methods for therapeutic application [18].

BIOAVAILABILITY AND PHARMACOKINETICS OF EXTRACTED COMPOUNDS

The pharmacological effectiveness of chemicals derived from herbal resources is largely dependent on their pharmacokinetics and tissue distribution patterns. For example, variations in the physiological state of Body factors like gender, age, illnesses, and outside stimuli can affect a drug or herbal medicine's oral bioavailability, tissue distribution, halftime (t1/2), maximum plasma concentration (Cmax), time to reach Cmax (Tmax), etc. These changes in intrinsic pharmacokinetic parameters will result in differences in the therapeutic effects of the medication. The pharmacokinetics of herbal medicines—how they are absorbed, distributed, metabolized, and excreted in the body—can be significantly influenced by multiple factors in clinical practice. Key factors include:

Physiological Factors: Age, gender, genetics, and health conditions can alter the body's handling of herbal compounds.

Herbal Medicine Characteristics: The chemical composition, formulation, and dosage form of herbal products affect their bioavailability and metabolism.

Drug-Herb Interactions: Concurrent use of pharmaceuticals or other herbs can lead to interactions that modify absorption or metabolism, often through effects on liver enzymes or transporters.

Environmental and Lifestyle Factors: Diet, smoking, alcohol intake, and other lifestyle choices can influence the pharmacokinetics of herbal compounds.

Pathological Conditions: Diseases affecting liver, kidney, or gastrointestinal function can impact the metabolism and clearance of herbal medicines [19].

Nutrient bioavailability is influenced by external factors like food composition and internal factors such as intestinal transit time and metabolism. A key internal factor is the molecular structure of bioactive compounds, which affects how they are absorbed in the gut. For example, most polyphenols, including flavonoids, exist in forms bound to sugars (glycosides) or polymers, which are not directly absorbable. These glycosides typically require enzymatic removal of their sugar components, often in the small intestine, to allow absorption of the aglycone parts. However, absorption sites vary—some compounds are absorbed in the small intestine, others in the colon. Larger molecules like oligomeric polyphenols must be broken down before absorption. Metabolism and conjugation of these compounds also impact bioavailability. While conjugation can help solubilize compounds for excretion, it can reduce the amount available in the bloodstream. Transport proteins like MRP2 can pump conjugated metabolites back into the intestine, while others like MRP1 help move them into circulation. Gut bacteria further modify polyphenols in the colon, sometimes creating more bioactive and bioavailable metabolites, such as equal from soy isoflavones, which exhibits stronger biological activity than its precursor [20]. Clinical trial studies of plant extracts with anti-inflammatory activity are research studies done on people to test how well natural plant-based substances can reduce or control inflammation in the body. These trials help check if the plant extracts are safe, effective, and can be used as medicine for treating inflammatory diseases [21]. A traditional Chinese herbal formulation containing ten herbs, marketed as Zemaphyte®, was studied for treating atopic dermatitis. In double-blind, placebo-controlled trials by Sheehan et al., the formulation showed significant improvement in both adults and children with atopic eczema, with many children maintaining benefits 12 months post-treatment. The herbal mix included Ledebouriella seseloides, Potentilla chinensis, Rehmannia glutinosa, and others. However, a later Chinese study by Fung found no difference between the formulation and placebo, possibly due to dosage, dropout rates, or racial differences. Traditional Chinese medicine emphasizes personalized treatment, contrasting with the fixed commercial formulation used in these studies, leaving the optimal herb combinations and doses uncertain. Separately, clinical trials on psoriasis found positive effects from Mahonia aquifolium, Indigo naturalis, and Aloe vera, while kukui nut oil showed modest improvement and Camptotheca acuminata gel significantly outperformed placebo and other formulations [22].

SAFETY CONSIDERATION AND TOXICITY OF EXTRACTS

Traditional medicinal herbs include various plant parts—such as aerial parts, flowers, fruits, leaves, seeds, stems, and underground parts like roots, bulbs, tubers, and rhizomes—used in forms like raw, fresh, dried, or extracts, sometimes as whole dried plants. They hold significant clinical, economic, health, and pharmaceutical value worldwide and are increasingly in demand. However, data on the quality, safety, and efficacy of many plants and their preparations remain limited, making quality assurance essential to ensure their safe and effective use.The historical use of herbal medicines highlights their potential, but modern science stresses the need for rigorous safety and efficacy testing. Unlike pharmaceuticals, herbal products often lack standardized dosages and may interact with other drugs, with some causing adverse effects. Regulatory bodies now focus more on ensuring the quality and safety of these products. While isolated plant compounds have shaped modern medicine, the holistic use of multiple plant components remains important. The herbal medicine industry has grown significantly, offering diverse products in alternative and complementary medicine, driving increased demand for thorough evaluation of their safety and effectiveness [23]. Plant-based medicines, whether used as crude extracts or purified compounds, are widely employed in the prevention and treatment of various diseases (Singh et al., 2022). However, concerns remain regarding their manufacturing standards, chemical composition, and potential toxicity (Ekor, 2014). Approximately 10% of vascular plants are used medicinally, many of which contain toxic secondary metabolites such as alkaloids, phenolics, terpenoids, tannins, saponins, cyanogenic compounds, and certain amino acids (Salmeron-Manzano et al., 2020; Dai & Mumper, 2010). The absence of well-defined therapeutic-to-toxic dose boundaries further complicates their safe use. Consequently, there is growing support from health organizations and complementary and alternative medicine (CAM) practitioners for more research into the safety and toxicology of medicinal plants [24]. The legal status of herbal medicines varies widely across countries. In some regions, phytomedicines are well-regulated; in others, they are classified as food products, and no therapeutic claims are permitted. Many developing countries rely heavily on traditional herbal knowledge but often lack robust legal frameworks to incorporate these products into existing drug laws. Regulatory classification may depend on factors such as inclusion in national pharmacopoeias, prescription requirements, therapeutic claims, ingredient restrictions, or intended duration of use. Some systems differentiate between "approved" products, which undergo scientific evaluation, and "recognized" products, which may be marketed without such assessment. Globally, legislative approaches range from treating herbal medicines under the same regulatory standards as conventional pharmaceuticals to granting partial or full exemptions. In some cases, only basic registration or marketing authorization is required. In countries lacking formal regulation, special licensing systems are recommended to evaluate product quality, ensure safety, and implement post-marketing surveillance of adverse effects [25].

INNAVATION IN EXTRACTION TECHNIQUE

Future research should emphasize eco-friendly and efficient extraction methods such as supercritical CO_2, microwave-assisted, ultrasound-assisted, enzyme-assisted, and continuous-flow technologies. These approaches can improve yield, maintain thermolabile compounds, and reduce solvent use. Linking extraction fingerprints with bioactivity is essential for reproducibility and quality control. However, significant gaps remain in scalability, environmental impact assessments, and inter-laboratory reproducibility[26].

INTEGRATING MODERN AND TRADITIONAL APPROCHES

New extraction techniques have emerged in response to the growing interest in bioactive compounds from natural sources, particularly those with anti-inflammatory activity. Unlike conventional methods, these approaches are designed to be more environmentally friendly while efficiently isolating phytochemicals—plant-derived bioactive compounds with significant health benefits and industrial applications. Advanced technologies such as supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, instant controlled pressure drop, pressurized liquid extraction, and negative pressure cavitation have demonstrated improved yields, reduced solvent consumption, and enhanced sustainability. Efficient extraction of anti-inflammatory phytochemicals enables their use in therapeutic applications, functional foods, and nutraceuticals. Integrating phytochemical extraction with biorefinery concepts supports circular economy principles and zero-waste valorization of plant biomass. This review examines recent advancements in green extraction techniques, emphasizing their role in isolating anti-inflammatory compounds, enhancing human health, and promoting environmental sustainability [27].

CLINICAL RESEARCH AND STANDARDIZATION

Clinical development requires a pipeline starting from Phase I pharmacokinetic and safety studies to randomized controlled trials (RCTs) in diseases like arthritis, colitis, and psoriasis. Establishing quality control through multi-marker chemical and bioassay standards, along with open-access reference materials and toxicology packages, is critical for global acceptance. Current gaps include variable trial designs, inconsistent endpoints, and lack of harmonized international regulatory standards [28].

POTENTIAL FOR PERSONALIZED HERBAL MEDICINE IN INFLAMMATORY DISEASE MANAGEMENT

The potential of personalized herbal medicine in managing inflammatory diseases lies in tailoring treatments to individual patient profiles, including genetic variations, cytokine signatures, and gut microbiome composition. Multi-component herbal extracts can target multiple inflammatory pathways, and integrating pharmacogenomics, metabolomics, and microbiome data can optimize efficacy while minimizing adverse effects. AI-driven platforms and companion diagnostics can guide selection of specific herbal formulations for each patient, enabling precision therapy. Although promising, biomarker-informed clinical trials of herbal interventions remain limited, highlighting a critical area for future research to advance personalized, mechanism-based treatment strategies for conditions such as rheumatoid arthritis, ulcerative colitis, and psoriasis [29].

CONCLUSION

In summary, herbal medicine represents a promising and multifaceted approach to managing inflammatory diseases, offering therapeutic benefits through diverse bioactive compounds such as flavonoids, terpenoids, and alkaloids. The efficacy and safety of herbal treatments are profoundly influenced by the extraction methods employed, which determine the quality, concentration, and bioavailability of the active constituents. Modern extraction technologies—including supercritical fluid extraction, ultrasound-assisted, and microwave-assisted techniques—provide more efficient and selective isolation of anti-inflammatory agents, enhancing their clinical potential. Despite encouraging preclinical and clinical evidence, challenges remain regarding standardization, safety, and regulatory oversight of herbal products. Addressing these gaps through rigorous research, improved extraction protocols, and comprehensive clinical trials is essential to establish herbal medicine as a reliable alternative or adjunct to conventional anti-inflammatory therapies. Furthermore, integrating traditional herbal knowledge with cutting-edge scientific advancements and exploring personalized approaches tailored to individual patient profiles could revolutionize inflammation management. Ultimately, advancing extraction technologies and harmonizing herbal medicine standards will be critical to unlocking the full therapeutic potential of natural products in combating chronic inflammatory diseases**.**

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