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Narrative Review of Anti-Inflammatory Phytochemicals

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ABSTRACT

Phytochemicals are naturally occurring plant-derived compounds that play significant roles in modulating inflammatory processes through diverse cellular and molecular mechanisms. Chronic inflammation contributes to the development of diseases such as cardiovascular disorders, rheumatoid arthritis, diabetes, Alzheimer's disease, and cancer. Major classes of anti-inflammatory phytochemicals, including flavonoids, terpenoids, alkaloids, and phenolic acids, exert their activity by regulating transcription factors (NF-κB, STAT, MAPK), enzymes (COX-2, iNOS, LOX), and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Evidence from preclinical, animal, and human studies highlights the therapeutic potential of phytochemicals in reducing inflammation and restoring homeostasis. Fruits, vegetables, herbs, and spices are abundant dietary sources, while advanced formulations such as nanoparticles and liposomes are improving their solubility and bioavailability. Although promising, challenges remain regarding optimal dosage, safety, drug interactions, and regulatory oversight. Future research should emphasize clinical trials, novel delivery systems, and emerging phytochemicals with enhanced therapeutic profiles to support their integration into conventional and complementary medicine.

Keywords: Anti-inflammatory phytochemicals**,** Flavonoids, Molecular targets, Bioavailability, and Chronic inflammation.

INTRODUCTION

Phytochemicals are naturally occurring biologically active compounds synthesized by plants that exhibit a wide range of biological properties, including antioxidant and anti-inflammatory effects [1-4]. They are commonly found in fruits, vegetables, cereals, and spices, into which they are ubiquitously incorporated as flavorings and colorings. The most important groups of anti-inflammatory phytochemicals are flavonoids, terpenoids, alkaloids, and phenolic acids [5-7]. By regulating cellular and molecular pathways of inflammation, phytochemicals exert beneficial effects in animal models of prevalent inflammatory diseases and represent promising candidates for human clinical trials. Since sustained inflammation is also associated with an increased risk of cancer, studies investigating the anticancer effects of some phytochemicals may expand their therapeutic potential [8-12].

Role of Inflammation in Disease

Living organisms employ biochemical cascades to respond to various stimuli, such as infection, toxins, and tissue injury; these often disrupt homeostasis until the organism adapts or the insult ceases. A protective adaptation, inflammation supplies host defense against infectious or foreign agents [13-16]. Innate immune responses become prolonged and dysregulated, then become chronic inflammation, which contributes to several disease processes. Inflammation is the immune system's attempt to heal and restore tissue following injury [1]. It is typically divided into two phases: acute and chronic. Acute inflammation is self-limiting and characterized by fluid exudation and neutrophil infiltrates, whereas chronic inflammation is prolonged and distinguished by the presence of lymphocytes and macrophages and the proliferation of blood vessels and connective tissue [17-21]. Under normal circumstances, acute inflammation is rapidly turned off because it can become life-threatening. When inflammation persists despite the removal of the noxious stimulus, the inflammation is considered chronic. The prolonged presence of the inflammatory cells entails persistent secretion of cytokines, chemokines, and reactive oxygen

species, which can result in the alteration of normal physiological processes. This persistent inflammation has an important role in the development of several diseases. Chronic inflammation is the cause of many different diseases, including rheumatoid arthritis, Alzheimer's disease, and cardiovascular disease [22-25].

Mechanisms of Action of Anti-Inflammatory Phytochemicals

Phytochemicals have been demonstrated to influence anti-inflammatory mechanisms through modulation of a number of cell signaling cascades, including those of NF-κB, STAT, and Nrf-2, which are key targets for the development of new anti-inflammatory drugs [26-30]. As a result, many phytochemicals exert anti-inflammatory effects by suppressing inflammatory mediators, pro-inflammatory cytokines, COX-2, and iNOS expression, and oxidative stress caused by reactive oxygen species (ROS) [1]. Given that inflammation is a biological response to harmful stimuli characterized by complex interplay among soluble factors and cellular responses, phytochemicals that inhibit inflammation have potential utility in preventing inflammation-related disorders and promoting well-being [31-33].

Cellular Pathways

Inflammation contributes to chronic diseases such as AD, SLE, RA, and diabetes. In response to inflammatory stimuli, large numbers of pro-inflammatory mediators and cytokines are secreted by macrophages and other immune cells [34-36]. No effective therapies currently exist that can cure inflammatory diseases; therefore, suppressing chronic inflammation has become an important therapeutic objective. Many phytochemicals inhibit inflammatory mediators and pro-inflammatory cytokines by affecting key intracellular pathways, including NF-κB, STAT, and Nrf-2. Since these pathways represent primary targets in inflammation, modulating them is central to the anti-inflammatory actions of phytochemicals [37].

Molecular Targets

By targeting intracellular signaling pathways, phytochemicals suppress the expression of pro-inflammatory cytokines, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and the production of reactive oxygen species (ROS). These molecular targets are central to the maintenance and progression of inflammatory states, and their modulation by phytochemicals underpins the observed reduction in inflammatory responses [38-40].

Cellular Pathways

Phytochemicals exhibiting anti-inflammatory activity regulate inflammation through several intracellular mechanisms by suppressing the activation of pro-inflammatory transcription factors such as nuclear factor κB (NF-κB), mitogen-activated protein kinases (MAPK), and signal transducer and activator of transcription (STAT) [41-44]. NF-κB is activated by pro-inflammatory compounds, including nuclear factor of activated T cells (NFAT), activator protein-1 (AP-1), and MAPK, leading to the production of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS), an essential pro-inflammatory mediator. On its activation, the NF-κB regulatory subunit p65/p50 is phosphorylated, resulting in the synthesis of pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2), iNOS, and lipoxygenase (LOX) in inflammatory disorders. MAPK, a serine/threonine protein kinase, has three isoforms: extracellular signal-regulatory kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 that regulate cell proliferation, differentiation, migration, and apoptosis in response to extracellular stimuli and inflammatory responses. The phosphorylation of MAPK activates pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), which aggravate inflammatory processes [45-47].

Molecular Targets

Cellular signaling pathways provide a broad overview of mechanisms involved in inflammation. More specifically, the following molecules constitute major molecular targets of anti-inflammatory phytochemicals [48-52]. Cytokines regulate the amplitude and duration of immune responses through binding to specific receptors. Pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and IL-6 play important roles in the pathology of many chronic inflammatory diseases. Similarly, chemokines induce chemotaxis in nearby responsive cells, and excessive production is thought to lead to chronic inflammation [53-57]. Thus, the reduction or inhibition of these pro-inflammatory proteins is a key anti-inflammatory mechanism of phytochemicals [58-60]. Enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX) catalyze the production of eicosanoids, which are important signaling molecules in the inflammatory response. Many anti-inflammatory drugs (nonsteroidal anti-inflammatory drugs, NSAIDs) target the inhibition of COX-2; several phytochemicals also show strong suppressive activities. Phospholipase A2 (PLA2) acts upstream by releasing arachidonic acid (AA) from phospholipids and thus controls the substrate supply to COX and LOX enzymes [61]. Transcription factors regulate the expression of many inflammatory genes. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein-1 (AP-1) are key pro-inflammatory factors, whereas peroxisome proliferator-activated receptor gamma (PPAR-γ) exhibits protective, anti-inflammatory functions in a variety of cell types [1].

Major Classes of Anti-Inflammatory Phytochemicals

Major groups of phytochemicals possessing potent anti-inflammatory effects include flavonoids, terpenoids, alkaloids, and phenolic acids [1]. The flavonoid group comprises a large family of polyphenolic compounds that help increase liver superoxide dismutase and possess antioxidant and free radical scavenging activities. Over 9000 flavonoids with various derivatives are distributed throughout the plant kingdom. The terpenoid group is the largest phytochemical group. Several terpenoids exert anti-inflammatory activities by inhibiting pro-inflammatory mediators, including cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and interleukin-1β. Alkaloids are complex organic compounds containing nitrogen in a ring structure, providing protective roles in plants during inflammation. Several alkaloids effectively inhibit inflammatory mediators downstream of nuclear factor-kappa B (NF-κB) signaling pathways. Phenolic acids are a group of aromatic compounds containing one carboxylic acid and constitute a major class of plant-derived anti-inflammatory agents [3]. Similar to flavonoids, phenolic acids exert free radical scavenging and antioxidant activities [3]. Broadly speaking, the effectiveness of phytochemicals in treating chronic inflammatory diseases depends on their stability in and bioavailability to the circulatory system. Naturally, the stomach and intestine degrade most ingested phytochemicals. Dietary phytochemicals such as flavonoids are usually present in significant quantities and absorbed through the gut when ingested as part of whole fruits and vegetables. Consumption of fruits and vegetables is associated with health benefits and reduced risk of developing diseases involving inflammation. Most anti-inflammatory phytochemicals are currently consumed within the diet, which constitutes approximately 15% of total intake. Mikania laevigata, known as guaco, produces the flavonoids kaempferol and quercetin, which exhibit strong anti-inflammatory activities [3]. Garlic produces allicin, a sulphur-containing compound that modulates prostaglandin synthesis and protects against the common cold and throat infections through anti-inflammatory activity. Ginger possesses pungent components such as 6-gingerol that exhibit anti-inflammatory effects. Extracts of devil's claw roots contain several iridoid glycosides that display anti-inflammatory activity [1, 3]. Finally, turmeric and green tea also exhibit significant anti-inflammatory effects through their active phytochemical compounds.

Flavonoids

Flavonoids constitute a major group of natural products widely distributed in fruits, vegetables, grains, and various beverages and spices [4]. They consistently demonstrate a broad range of anti-inflammatory properties in experimental systems. The anti-inflammatory activity derives mainly from inhibitory effects on eicosanoid-generating enzymes, interactions with pro-inflammatory transcription factors, mitogen-activated protein kinases, and pro-inflammatory cytokines [4]. Multiple inhibitory mechanisms suggest a complex, synergistic approach to downregulate inflammation rather than simple, selective inhibition.

Terpenoids

Terpenoids constitute a large and diverse group of plant metabolites with noteworthy anti-inflammatory activity. These compounds are industrially attractive due to their bioactivity and relative safety compared with synthetic agents. Terpenoids act on various molecular targets linked to inflammation, inhibiting cytotoxicity induced via nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, as well as the activation of proinflammatory cytokines (interleukin-1β [IL-1β], tumor necrosis factor [TNF-α], IL-6, interferon-γ) and enzymes (inducible nitric oxide synthase [iNOS], cyclooxygenase-2) [5]. For example, diterpenes such as tanshinones, isolated from the roots of Salvia miltiorrhiza, reduce the expression of IL-12 in lipopolysaccharide (LPS)-activated macrophages. By simultaneously inhibiting both the production and gene expression of inflammatory mediators, terpenoids exert potent anti-inflammatory effects. Numerous studies have demonstrated that terpenes and terpenoids possess strong potential as alternative treatments for inflammatory diseases; these compounds employ different signaling pathways and exert a pleiotropic effect, indicating that they could be more effective than existing medications. Nonetheless, comprehensive investigations are required to evaluate clinical efficacy and safety, including the determination of safe dosage levels. Observations from in vitro experiments and animal models are not universally applicable to humans; therefore, controlled clinical trials are essential. Additionally, the medicinal benefits of terpenes may be compromised by low solubility and high instability, prompting interest in encapsulation within nanocarriers as a promising strategy [5].

Alkaloids

Alkaloids, a diverse group of basic nitrogen-containing compounds, exhibit significant physiological effects at low concentrations and have been identified as potent anti-inflammatory agents. Key plant families containing bioactive alkaloids with anti-inflammatory properties include Solanaceae, Leguminosae, Apocynaceae, Liliaceae, Papaveraceae, Rutaceae, and Ranunculaceae [6]. Tetrandrine, a bisbenzylisoquinoline alkaloid isolated from Stephania tetrandra, is traditionally employed in the treatment of rheumatic diseases and silicosis. Its anti-inflammatory activity is attributed to inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways.

Berbamine suppresses prostaglandin E2 production and modulates natural killer cell function, contributing to its anti-inflammatory effects. In vitro, tetrandrine attenuates inflammatory cytokine release, lipid mediator synthesis, histamine secretion, and tumor necrosis factor-alpha expression [6]. Extracts from Buxus papillosa and Buxus sempervirens demonstrate anti-inflammatory activity, notably in the context of rheumatism and dermatological conditions. Ethanolic extracts of Adhatoda vasica exert significant anti-inflammatory effects across multiple experimental models, while alkaloids derived from Sida cordifolia display pronounced anti-inflammatory activity in diverse animal assays [6]. The structural and functional diversity of alkaloids renders them promising candidates for therapeutic development against inflammatory and neurodegenerative diseases. Leading compounds such as harmine, berberine, and galantamine have emerged as potential agents due to their complementary anti-inflammatory and acetylcholinesterase inhibitory activities [7]. Comprehensive preclinical evaluations encompassing clinical trials, pharmacokinetics, safety profiles, and mechanistic studies remain necessary to fully characterize their health effects and establish clinical utility. Toxicological considerations are particularly pertinent, as numerous alkaloids exhibit adverse effects at elevated concentrations. Consequently, investigations into combinatorial regimens incorporating alkaloids alongside existing FDA-approved drugs may enhance long-term therapeutic efficacy for inflammation and neurodegeneration [7].

Phenolic Acids

Phenolic acids, a class of non-flavonoid polyphenolic compounds, comprise cinnamic acid derivatives and benzoic acid derivatives. These compounds are ubiquitously distributed in fruits and vegetables and frequently occur in plants as conjugated forms with carboxylic or organic acids [8]. Cinnamic acid derivatives are widely found in many fruits and vegetables. Naturally occurring examples of such derivatives include caffeic acid, ferulic acid, and chlorogenic acid [9]. Among the cinnamic acid derivatives, cinnamic acid exhibits anti-inflammatory effects by inhibiting the expression of iNOS and COX-2, as well as the phosphorylation of proteins involved in the NF-κB and MAPK pathways. Caffeic acid, a precursor of chlorogenic acid, also suppresses the NF-κB and MAPK signaling pathways by reducing the production of IL-1β, IL-6, and NO in LPS-stimulated macrophages. Ferulic acid downregulates the production of cytokines and chemokines, including TNF-α, IL-1β, and MCP-1, by inhibiting the ERK1/2 and p38 MAPK pathways. Chlorogenic acid suppresses the production of PGE_2, iNOS, and COX-2 through the inactivation of the NF-κB signaling pathway [8, 9].

Sources of Anti-Inflammatory Phytochemicals

Fruits, vegetables, and dietary plants, herbs, and spices provide important sources of phytochemicals with anti-inflammatory activity. Many edible plants, including a large number of fruits and vegetable sources, provide important sources of phytochemicals with anti-inflammatory activity. Among fruits, citrus fruits provide a number of important anti-inflammatory constituents, including certain hydroxycinnamic acids and flavanones such as hesperidin and eriocitrin [3]. In vegetables, many Allium species have anti-inflammatory activity. For instance, garlic contains several organosulfur compounds. Brassica species, including broccoli, Brussels sprouts, and cabbage, contain glucosinolates and hence isothiocyanates with anti-inflammatory properties [1]. Other vegetables, such as eggplant, green pepper, and tomato, contain phenolic acid derivatives with anti-inflammatory activity. Among cereals, rice bran and maize provide sources of anti-inflammatory phytochemicals.

Fruits

Several fruits are good sources of anti-inflammatory phytochemicals. A handful of well-studied examples illustrate the diversity of fruit phytochemicals. Blueberries, Cranberries, Blackcurrants, and Strawberries all contain several anthocyanins, although in different abundances. Blueberries have delphinidin and malvidin derivatives, and blackcurrants also have cyanidin derivatives [10]. The plums from Japanese and European plum cultivars have different phenolic profiles. Actinidin, the main proteinase in kiwifruit, has anti-inflammatory and anti-arthritic properties. Fig and Olive fruits contain scopoletin, psoralen, o-coumaric acid, and gallic acid. These agents, alone or in combination, inhibit COX-2, TNF-, IL-6 and IL-1. [11].

Vegetables

Vegetables are vital for health and a significant source of phytochemicals for humans. These are biologically active, nonnutritional secondary metabolites produced by the plants. Dietary phytochemicals not only provide colour and flavour to food but also promote health benefits such as anti-inflammatory, antimicrobial, antioxidant, antiviral, anti-allergic, anticancer, and wound-healing activities [11]. Cruciferous vegetables (such as broccoli, cabbage, and Brussels sprouts) contain the phytochemicals sinigrin, glucoraphanin, and glucoiberin, which exhibit potential anti-inflammatory properties. The carotenoid pigment deposited in sweet potatoes, β-carotene, is an important antioxidant. Vegetables like potatoes and onions have high polyphenol, micronutrient, and carotenoid contents that contribute to their anti-inflammatory potential [10]. Dietary polyphenols (apigenin and isochlorogenic acid) also have anti-inflammatory activities. Saponins are abundant in vegetables such as spinach and lettuce. An

important polyphenol contained in parsley, luteolin, is a flavonoid with various health-beneficial properties, including anti-inflammatory, antidiabetic, antioxidant, and anticancer effects [10]. Solanine is a steroidal alkaloid mainly extracted from vegetables such as potatoes and tomatoes. Ginger contains the phytochemicals zingerone, gingerol, and shogaol, which have potential anti-inflammatory activity [11].

Herbs and Spices

In general, herbs and spices are a rich source of anti-inflammatory phytochemicals. Essential oils derived from herbs and spices are a mixture of phytochemicals, and the quantity and composition of the phytochemicals often vary with species and even cultivar [3, 9]. Ginger (Zingiber officinale) rhizome essential oil has been widely used as a spice all over the world, and the rhizome contains high amounts of bioactive phytochemicals that exhibit potent anti-inflammatory activity [12]. Thymoquinone is found in the oil extracted from the seeds of Nigella sativa, and it exerts anti-inflammatory activity mainly by inhibiting cyclooxygenase and lipoxygenase activities. The rhizomes of turmeric (Curcuma longa) and galangal (Alpinia officinarum) have also been used as spices, and their oils have been analyzed by chromatographic techniques and found to be enriched in terpenoids [3, 9, 12]. The Indonesian clove and clove bud oils contain high concentrations of eugenol, which can inhibit the synthesis of prostaglandin and pro-inflammatory cytokines.

Clinical Evidence of Anti-Inflammatory Effects

Clinical studies have provided evidence for the anti-inflammatory activities of phytochemicals. A luteolin-rich extract of Chrysanthemum morifolium flowers administered to male volunteers exposed to prolonged oxidative stress reduced plasma levels of C-reactive protein (CRP) and interleukin (IL)-6 [1]. Subjects with moderate gingivitis who received a cranberry juice enriched with polyphenols showed decreased levels of proinflammatory mediators, including matrix metalloproteinases (MMPs), IL-1β and -6, and prostaglandin E2 (PGE2) [3]. Similar findings have been noted in pre-clinical in vivo models. Piceatannol, an analogue of resveratrol, suppressed paw swelling and reduced the production of pro-inflammatory cytokines in a rat model of collagen-induced arthritis. In a model of acute lung injury, treatment with psydraxin, an iridoid monoterpene, inhibited MMP activity as well as secretion of TNF-α and IL-6 and decreased neutrophil infiltration into lung tissue. Such studies support the anti-inflammatory potential of phytochemicals, underscoring their promise as therapeutic agents for inflammation-related conditions [1, 3].

Human Trials

Many phytochemicals demonstrate notable anti-inflammatory efficacy in human trials. Curcumin administration (500–8,000 mg daily) for various disorders induces significant reductions in plasma tumor necrosis factor (TNF-α), interleukin (IL)-6, IL-8, and C-reactive protein (CRP) cytokine levels [3]. Colchicine may provide clinical anti-inflammatory protection in familial Mediterranean fever (1 mg/d) and acute pericarditis (0.5–1.0 mg/d). It reduces serum IL-18 in adult-onset Still's disease (1 mg/d for 4 weeks) and diminishes high-sensitivity CRP (hs-CRP) in individuals at risk of cardiovascular disease (CD) over 3 months. Resveratrol doses ranging from 5 to 500 mg daily improve inflammatory conditions in colorectal cancer, diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD) through the downregulation of IL-6, TNF-α, and IL-1β in plasma and leucocytes. Capsaicin doses between 0.075% and 0.1%, administered over 2–12 weeks, elicit transient pro-inflammatory responses followed by long-term anti-inflammatory and analgesic outcomes for neuropathic and osteoarthritic pain, spinal cord injury, and musculoskeletal disorders. Epigallocatechin-gallate (EGCG) consumption (400–800 mg daily) reduces plasma CRP, TNF-α, and IL-6 in rheumatoid arthritis, multiple sclerosis, and ulcerative colitis. Quercetin intake of 100–500 mg daily alleviates oxidative stress, exercise-induced inflammation, and inflammatory symptoms associated with prostatitis-related chronic pelvic pain syndrome [3].

Animal Studies

Human trials are indispensable for obtaining the definitive evidence required for the application of anti-inflammatory phytochemicals [3]. Historically, multiple preclinical studies have proposed the anti-inflammatory potential of such compounds in animal models, predating investigations involving human subjects. Consequently, the present section introduces evidence of anti-inflammatory phytochemicals derived from animal models of inflammatory diseases [3].

Safety and Toxicity of Phytochemicals

A wide variety of phytochemicals with anti-inflammatory capacity have been identified to date [1]. Although plants produce structurally diverse types of phytochemicals, the classes of phytochemicals exhibiting potent anti-inflammatory activity are limited. These compounds can be broadly classified as polyphenols, saponins, alkaloids, and terpenoids, based on their chemical structure. An important feature of anti-inflammatory phytochemicals is that they suppress inflammatory responses involving various cellular pathways and molecular targets [1]. Over-the-counter supplements of plant-derived phytochemicals are used otherwise as dietary ingredients (usually in

powder, capsule, tincture, tea, or extract form) for their anti-inflammatory properties. However, perhaps the most important degree of freedom to quantify anti-inflammatory phytochemicals is dosage and overall availability within commercial products [1]. These phytochemicals can be toxic when consumed beyond the body's physiological capacity, and at certain doses, phytochemicals may interact with other drugs. For the clinical use of phytochemicals, the adequate dosage and the corresponding benefits and risks must be assessed to establish the required safety level and reduce undesired complications [1].

Dosage Considerations

Before discussing half maximal inhibitory concentration or dosage, it is important to understand the mechanisms of toxicity [2]. The dosage at which a chemical compound will be toxic depends on various factors. From the pharmacokinetics perspective, the toxic dose should be higher than the dose necessary for the compound to permeate the envelope. Alongside this, metabolism and excretion rates need to be considered, typically obtainable using in silico tools. Toxicity could stem from either the parent compound or the metabolite [6]. Toxicity and permeability must be considered during drug design or bioengineering. Equally important is the correlation of molecular mechanisms to biological response to accurately determine the dosage that elicits the lowest toxicity with the desired level of activity. Several methods in machine learning can assist with these correlations [7].

Potential Interactions

The therapeutic value of anti-inflammatory phytochemicals raises concerns about their potential interactions with synthetic drugs. Synthetic drugs commonly employed in anti-inflammatory settings, including fluoxetine and rofecoxib, are known to cause adverse drug reactions, and their concurrent administration with phytochemicals could have unforeseen consequences [1]. Consequently, it is crucial to address the possibility of interactions between phytochemicals and pharmaceuticals such as simvastatin, chlorzoxazone, theophylline, or caffeine for a comprehensive understanding of their combined effects in treatment settings. Alterations to cytochrome P450 caused by phytochemicals can hinder drug exposure and efficacy, affecting clinical outcomes. Therefore, research initiatives should prioritize clarifying the scope and nature of phytochemical-drug-drug–drug interactions to inform safe and effective therapeutic strategies [1].

Regulatory Aspects of Phytochemical Use

Phytochemicals represent a valuable source of compounds with interesting biological activities and an important field of future studies and applications. Several interesting anti-inflammatory phytochemicals were identified and partially characterized during the last years. They can modulate key checkpoints of cellular and molecular inflammatory mediators in in vitro and in vivo models, but they must still be confirmed in clinical trials [1]. Data from ongoing studies are awaited, and the study of new phytochemicals may offer novel sources of anti-inflammatory molecules for pharmaceutical, nutraceutical, and food applications [1, 3]. Regulations for phytochemical use are well established worldwide, with specific lists of phytochemicals and application fields. In the USA, the Food and Drug Administration (FDA) established specific regulations for phytochemicals in foods, food additives, drugs, dietary supplements, and cosmetics [3].

FDA Regulations

The U.S. Food and Drug Administration (FDA) has implemented regulations governing the use of phytochemicals in cosmetics since 1938 [3]. Some of the widely utilized anti-inflammatory compounds found in plants also appear on this list. Both the FDA and the European Food Safety Authority (EFSA) have established guidance documents for community herbal monographs and lists of herbals permitted in food supplements, outlining regulations for food contact substances in the United States and conditions of use for various countries within the European Union [1, 3]. These regulatory frameworks provide essential information on the usage of anti-inflammatory phytochemicals in supplements or foods to maintain or improve health [1].

Global Perspectives

Medicinal plants and isolated phytochemicals exhibit anti-inflammatory activity and have been widely used in traditional medicine to treat a broad range of inflammation-related diseases. Interest in the anti-inflammatory potential of phytochemicals has increased considerably, partly because of the adverse effects of anti-inflammatory drugs and the ineffectiveness of some synthetic agents [3]. Specific phytochemicals with anti-inflammatory activity include catechins, curcumin, stilbenes, flavonoids, phenolic acids, terpenoids, and alkaloids. Various anti-inflammatory mechanisms of action have been reported, with many phytochemicals modulating nuclear factor (NF)-κB, mitogen-activated protein kinase (MAPK), and Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling pathways. Some downregulate the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 [1]. Phytochemicals with anti-inflammatory activity are found in numerous herbal medical products and common foods, such as fruits, vegetables, spices, cereals, and beverages. Further

investigation of the anti-inflammatory potential of phytochemicals, especially newly discovered compounds and those with limited experimental and clinical evidence of efficacy, is warranted [1, 3].

Future Directions in Research

The development of anti-inflammatory preparations containing phytochemicals still offers considerable potential for the future. New phytochemicals and herbal extracts continue to be identified, alongside new delivery systems for phytochemicals such as gingerol and curcumin [3]. The exploration of plant products remains a strategic focus for discovering novel anti-inflammatory drugs despite extensive ongoing research in inflammatory disorders and the pharmaceutical industry [3].

Emerging Phytochemicals

Advances in analytical chemistry and biotechnology continue to enhance the identification of novel phytochemicals with anti-inflammatory activities. Therefore, exploration of emerging phytochemicals and their delivery systems is increasingly important as an effective and efficient approach to address inflammation-related health issues. A few recent examples are summarized here [3]. Quassinoids are natural triterpenoids with an open A-ring found mainly in the Simaroubaceae family and some Rutaceae plants [1]. They have long been used in traditional medicine and as edible plants. Several quassinoids exhibit anti-inflammatory activity by suppressing the production of pro-inflammatory cytokines and chemokines. For instance, ailanthone inhibits lipopolysaccharide-induced NO, PGE2, and IL-6 production and suppresses NF-κB and STAT3 signaling pathways. Additionally, ailanthone demonstrates protective effects against Aβ-caused neurotoxicity and LPS-induced acute lung injury. Phlorotannins are marine algal polyphenols in the brown alga dominant order Fucales. These molecules are located within vesicles and secretory canals of brown algae, but low solubility and bioavailability have limited their analysis. Phlorotannins also exhibit anti-inflammatory activity through in vitro and in vivo models via NF-κB/MAPK, Nrf2/HO-1, and inflammasome signaling pathways [1, 3]. Malabaricone C is a phenylacylphenol (PPAP) found in the genus Myristicaceae. It possesses anti-inflammatory, anti-bacterial, antioxidant, and hepatoprotective activities, although poor solubility limits its application. Malabaricone C reduces pro-inflammatory mediators, including NO, TNF-α, and COX-2, by inhibiting NF-κB activation. The compound also alleviates LPS/D-GalN-induced acute hepatitis in mice [1, 3]. The flavonoid apigetrin (apigenin-7-O-glucoside) is a glycosidic form of apigenin found in several plants. It demonstrates inhibitory effects against LPS-induced inflammation and oxidative damage. Research indicates that apigetrin suppresses pro-inflammatory mediators by regulating NF-κB and STAT signaling pathways and inhibits skeletal muscle atrophy mediated by ROS-induced NF-κB activation [2]. Incorporating emerging compounds with novel delivery systems enhances the successful stabilization and bioavailability of therapeutic phytochemicals. Technologies such as liposomes, nanoparticles, and self-nanoemulsifying drug-delivery systems are explored both in vitro and in vivo [3].

Novel Delivery Systems

Phytochemicals present in medicinal and dietary plants have been widely reported to possess therapeutic effects in chronic inflammatory diseases [4]. Nevertheless, the clinical implementation of most phytochemicals has not yet been successful because of their low solubility and poor bioavailability. Several biocompatible formulations and delivery systems have been engineered to improve stability, solubility, bioavailability, bioactivity, and targeted delivery of phytochemicals. Nanotechnology offers a wide variety of molecular carriers that allow highly effective delivery of phytochemicals [13] and enable the treatment of a broad range of pathological conditions with greater efficiency and fewer side effects [14]. The bioavailability of phenolic compounds depends on intestinal absorption. Different biocompatible formulations and innovative delivery systems have been formulated for efficient delivery of phenolics at the target site. Strategies include development of powders for direct dilution in water or juices and water-in-oil or oil-in-water emulsions to incorporate lifts in oily matrices [14].

CONCLUSION

Anti-inflammatory phytochemicals represent a promising class of natural agents with therapeutic potential against a wide spectrum of inflammation-related diseases. By targeting key signaling pathways, cytokines, and enzymes, they modulate the inflammatory response while offering additional antioxidant and protective effects. Evidence from clinical and experimental studies underscores their value as complementary strategies to conventional therapies. However, limitations such as poor bioavailability, potential toxicity at high doses, and drug–drug-drug-phytochemical interactions present critical challenges that must be addressed. Regulatory frameworks, advanced delivery technologies, and rigorous human clinical trials are essential to ensure their safe and effective application. Looking forward, the integration of emerging compounds with innovative delivery systems offers new opportunities to harness phytochemicals for personalized medicine and global health.

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