Chapter 42

Modulating the Inflammatory Signals with Phytomedicines: An Approach to Manage Inflammatory Diseases

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ABSTRACT

Inflammation is the first multifaceted innate immune response against infectious agents, leading to clearance of invaded microbes and repair of the damaged tissue. Binding of the pathogen receptors, such as PAMPs, with the immune cells causes the release of proinflammatory mediators that cause the migration of leukocytes at the infection site. However, excessive release of these cytokines and ROS leads to irreversible tissue damage and other life-threatening diseases, including metabolic disorders, cancer, and cardiovascular diseases. The classical therapeutic approach for treating inflammatory diseases includes COX inhibitors and glucocorticoids. However, these conventionally available drugs cause severe toxicity and complications. Thus, there is a need to explore effective and affordable alternatives that actively module the inflammatory signals. Phytomedicines are promising therapeutic options to treat inflammatory diseases, and several new medicines have been discovered from plant-derived secondary metabolites. Studies have shown that plants such as *Sorghum bicolor* and *Alepidea amatymbica* prevent the eicosanoid release and lower the symptoms of inflammatory disorders. Similarly, researchers have also successfully targeted the NF-κB, JAK-STAT, and PI3K/AKT/mTOR pathways using plant-derived polyphenols, alkaloids, and peptides to treat life-threatening inflammatory disorders. Most phytomedicines have low solubility and poor bioavailability, which can lower their effectiveness. Thus, other technologies should be considered to enhance the bioavailability of phytomedicines.

KEYWORDS
Inflammation, Cytokines, Drug Resistance, Phytomedicines, Efficacy

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INTRODUCTION

Inflammation is considered a highly dynamic process, activated as the first multifaceted innate response against microbial invasion or damage to the cell due to any external stimuli, leading to the repair of the damaged tissues and clearance of microbes or microbial products from the body. Inflammation is mediated by the activation of different immune cells that regulate the release of the chemokines responsible for cell chemotaxis, migration, and proliferation in a highly uniformed manner. Cytokines are the essential signalling proteins released by immune cells in response to inflammation and immune response. They can be further divided into two categories: pro-inflammatory (IL-1, IL-6, IL-15, IL-17, IL-23, and TNFα) and Anti-inflammatory cytokines (TGFβ, IL-4, IL-13, IL-10, and IFNγ). Exposure to pathogen-associated molecular patterns (PAMPs) or other pathogen-associated signals results in the release of proinflammatory mediators, leading to the activation of a complex cascade that ends with migration and penetration of leukocytes into the site of infection (Rauch et al., 2013). Uncontrollable or unregulated release of inflammatory markers such as cytokines and Reactive Oxygen Species (ROS) constitutes the primary cause of immune pathology, responsible for irreversible damage to multiple organs and other life-threatening diseases, including cancer, cardiovascular dysfunctions, and metabolic disorders (Bagad et al., 2013; Li et al., 2022). According to a report published by Global Health Metrics to understand the causes of mortality from 1980 to 2017, inflammation-associated disorders are responsible for 50% of all mortalities. Among these disorders, cancer, ischemic heart diseases, diabetes mellitus, chronic kidney diseases, and non-alcoholic fatty liver, are the most common inflammatory diseases (Roth et al., 2018). The classical therapeutic approach for treating inflammatory diseases includes COX inhibitors and glucocorticoids. However, these drugs, such as valdecoxib and rofecoxib, are associated with severe toxicity and complications, such as stroke, raised blood pressure, blurred vision, angioedema, and rashes (Arora et al., 2020; McEvoy et

al 2021; Stone et al., 2022).

To overcome the complications and toxicity associated with glucocorticoids and COX inhibitors, effective and affordable, alternatives should be explored. Phytomedicines are promising therapeutic option to treat inflammatory diseases and several new medicines also possess unique bioactive molecules, including phenol, flavonoids, alkaloids, carotenoids, and organosulfur compounds. Due to their anti-inflammatory properties, these compounds can treat different inflammatory diseases (Akhtar 2022). The harmonious blend of age-old botanical wisdom and meticulous scientific evidence has unveiled an exquisite tapestry of therapeutic possibilities, showcasing the profound potential of plants to yield a myriad of healing remedies.

Inflammation Associated Pathways and Modulation with Phytomedicines

The inflammatory response is managed by a wide variety of mediators that create intricate regulatory networks. These coordinated pathways are controlled by releasing different cell-signaling mediators, including Eicosanoids, Cyclooxygenases, and Lipoxygenases. Other important inflammation-associated signals include NF-kB signal transduction, JAK-STAT, MAPK pathway, P13K/AKT/mTOR pathway, and TNF-B/Smad pathways. Many studies have shown that chemotherapy and radiation can trigger this tumor-associated inflammatory response (Vyas et al., 2014; Brown et al., 2021). Thus, researchers should focus on phytomedicines and other natural products to treat inflammatory diseases. The below section explains the general mechanism of inflammatory pathways and their modulation with phytomedicines.

Eicosanoids: Their Role and Modulation

Eicosanoids are a group of enzymatically generated metabolites of 20-carbon polyunsaturated fatty acids (PUFAs). The biosynthesis of eicosanoids is usually initiated by the release of Arachidonic acid and phospholipaseA2 membrane from phospholipids. Arachidonic acid is then converted into different metabolites, including pro-inflammatory eicosanoids, such as prostaglandins, thromboxane, and leukotrienes. Maintaining a balance between anti-inflammatory and pro-inflammatory eicosanoids is crucial in the hallmark of inflammatory diseases. Severs studies have shown that plant extract of ginger root, Rhodiola rosea, and *Eleutherococcus lenticonus* causes the release of anti-inflammatory eicosanoids and is used to treat several inflammatory diseases, including arthritis, cancer, asthma, and cardiovascular diseases (Zick et al., 2011; Panossian Efferth et al., 2019; Jasemi et al., 2023). These plants downregulate the expression of genes, such as DPEP2, LTC4S, ALOX5AO, ALOX12, and receptor 3 gene (PTGER3) which are involved in the biosynthesis of the pro-inflammatory cytokines, leading to the inhibition of leukotriene, lipoxins, and prostaglandins signaling pathways, indicating their potential against inflammatory diseases (Jasemi et al., 2023).

Inhibition of COX and LOX pathways by phytomedicine is mediated by the active compounds present in plants. The most important active compounds that inhibit the release of eicosanoids include phenol, polyketides triterpenes, flavonoids, and cinnamic acid. Another study published by Pongprayoon et al. (1991) showed the inhibition of prostaglandins by Ipomoea, pes-caprae due to the presence of 2-hydroxy-4,4,7-trimethyl-1(4H)-naphthalene, mullein, eugenol, and 4-vinyl-guaiacol, indicating the potential application of plants against inflammatory diseases (Pongprayoon et al., 1991).

Cyclooxygenase Inhibition with Phytomedicine

The Cyclooxygenase (COX) enzyme system is an important signaling pathway that involves the conversion of Arachidonic acid into prostaglandins, which causes the activation of different pro-inflammatory metabolites. Prostaglandins are an important group of eicosanoids that are involved in pain sensation and induction of inflammation. These are two iso-enzymes of COX, i.e., COX-1 and Cox-2. COX-1 enzyme pathways cause the release of PGE2 and PGI-2, whereas COX-2 causes the release of thromboxane. Thromboxane causes vasoconstriction and stimulus for platelets aggregation at the site of inflammation. Many NSAIDs perform their function by inhibiting the release of prostaglandins by blockade of COX-1 and COX-2 Pathways (Norregaard et al., 2015). Several studies have shown that several plants contain active compounds that inhibit the cyclooxygenases and can be used to treat pain and relief from inflammatory diseases (Jager and Staden 2005; Akinloye at al., 2019; Termer et al 2021). According to research published by Akinloye et al. (2019), the flavanone from *Sorghum bicolor* can inhibit the activity of COX-2 and can be used to protect liver from damage due to inflammation.

Lipoxygenase Inhibition

Lipoxygenases are an important group of enzymes that catalyze the catalysis of Arachidonic acid into hydroperoxides, which are then converted into leukotrienes, eicosanoids responsible for the activation of other cells at the inflammation site. Leukotrienes also cause contraction of airway bronchial muscles, mucus production, and increase vascular permeability. Several plant extracts have been studied to prevent the conversion of Arachidonic acid into hydroperoxides by LOXs (Loncaric et al., 2021). Apiaceae (*Umbelliferae*), *Alepidea amatymbica*, and *Petroselinum crispum* are important plants that prevent the activation of LOXs and are used to treat several inflammatory diseases, including arthritis, CVDs, and cancer (Amiri and Joharch, 2016; Muleya et al., 2017; Danciu et al., 2018).

Several studies showed that green nanosynthesis with plant extracts inhibit the LOX pathway and reduces inflammatory diseases (Bakir et al., 2022; Ongtanasup et al., 2024). The LOX pathway inhibition by the plant extract can also be used to treat asthma. Activation of leukotrienes by the LOX pathway results in an increase in mucus production associated with the symptoms of asthma, bronchoconstriction, and formation of edema (Amaral-Machado et al., 2020). A review published by

Isabella Schneider and Franz Bucar (2005) demonstrates the application of different plan species to inhibit leukotriene release and treat asthma.

The below figure shows different pathways involved in the synthesis of eicosanoids and the possible mechanisms of action of plant extract against these eicosanoids.

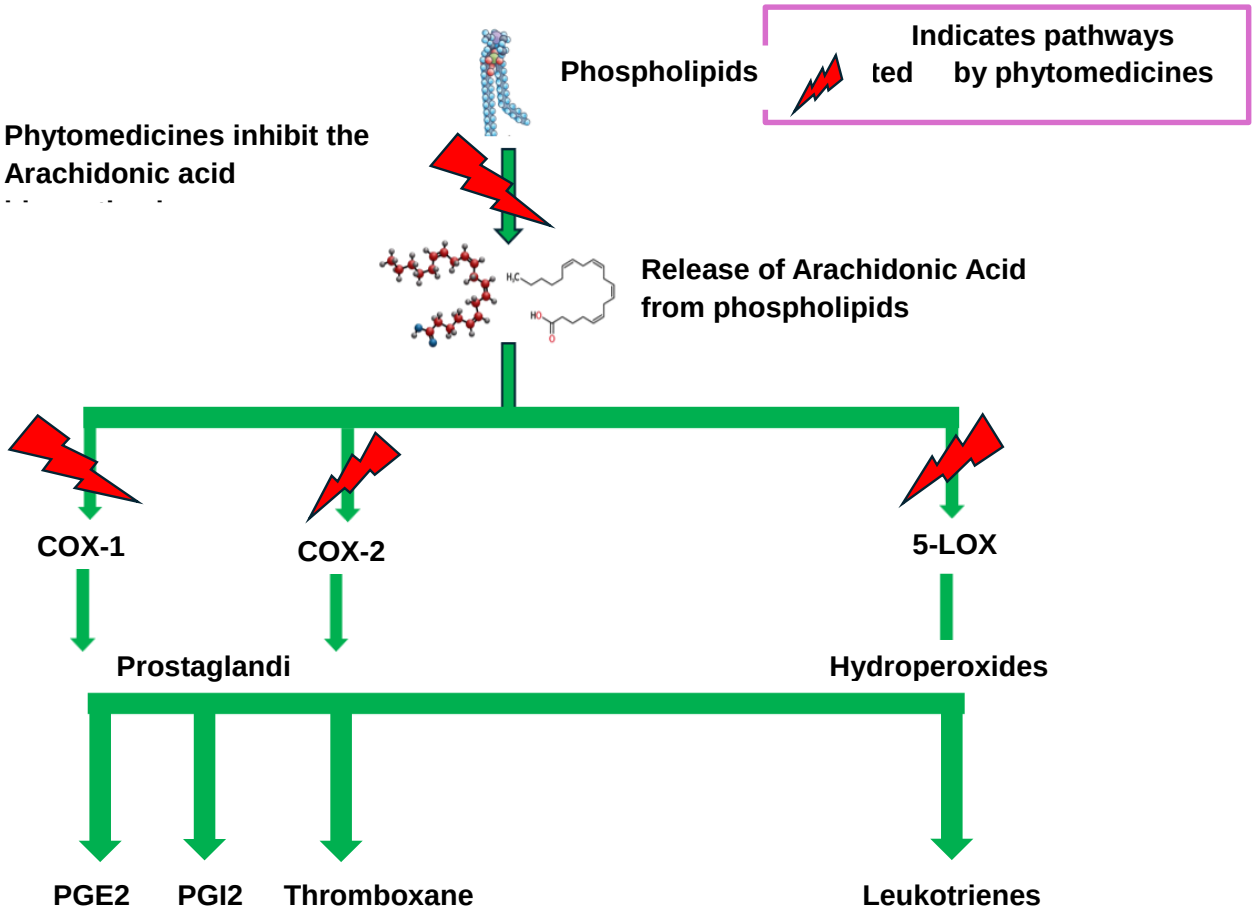

Fig. 2.1: Eicosanoids release in inflammation and possible pathways inhibited by phytomedicines

NF-κB Signal Transduction

The NF-κB is a crucial transcription factor that play a key role in inflammation and innate immunity. This transcription family comprises five major members, including NF-κB1, NF-κB2, RelA, RelB, and c-Re, and binds with the specific DNA element (as κB enhancer), increasing the transcription of target genes. Two important pathways mediate the activation of NF-κB: the canonical and alternate pathways. Canonical pathway of NF-κB signal transduction starts by the binding to the ligands of specific cytokine receptors, pattern recognition receptors (PRRs), TNF receptor (TNFR) superfamily members, as well as T-cell receptor (TCR) and B-cell receptor. On the other hand, non-canonical pathways respond to various stimuli, including TNFR.

Along with the mediating induction of various proinflammatory genes in innate immune cells, NF-κB also activates and differentiates inflammatory T cells (Liu et al., 2017). Several studies have also demonstrated the activation of inflammasomes by NF-κB. Activation of NF-κB signaling pathways is usually controlled by IKK, which contains two kinase subunits, IKKα (IKK1) and IKKβ (IKK2), and a regulatory subunit, IKKγ, also known as NEMO. IKKβ causes the activation of the canonical pathway by phosphorylation of IκBs. On the other hand, IKKα causes the phosphorylation of p-100, activating the non-canonical pathway (Lawrence, 2009). Lipopolysaccharide (LPS) induced inflammation is mediated by microbial invasion. Bacteria, especially gram-negative ones, release specific endotoxins, known as Lipopolysaccharides (LPS) which bind with Toll-like receptor 4 (TLR4) which in turn causes the release of cytokines from the immune cell. These cytokines activate the NF-κB, leading to the release of inducible nitric oxide synthase (iNOS), activation of the COX-2 pathway, and release of more cytokines. Thus, microbial invasion causes the activation of multiple inflammatory pathways and severe symptoms of disease (Gil et al., 2020). Figure 1.2 Illustrates the mechanism involved in the NF-κB pathway due to activation of receptors with different inflammatory ligands. Dysregulation of NF-κB has also been reported in different inflammatory diseases, especially autoinflammatory diseases, such as Alzheimer's disease (Snow and Albensi, 2016). NF-κB is a promising therapeutic target the neurodegenerative and chronic inflammatory disease. Several studies have provided convincing evidence that several phytomedicines with anti-inflammatory potential modulate the NF-κB to treat chronic inflammatory diseases, especially

cancer and CVD. A study published by Paur et al. demonstrates the modulation of NF-κB with 34 different plant extracts (Paur et al.,2008). Another study showed the anti-inflammatory potential of *Populus deltoides* by inhibiting the phosphorylation of NF-κB and inhibitor of Kappa Bα (IκBα). This plant extract also has potential to modulate other inflammatory pathways as well (Jeong and Lee, 2018). Similarly, Kim et al., (2020) successfully demonstrated the application of *Smilax guianensis* against LPS-induced inflammatory response.

Below table highlights the most important plants that modulate the NF-κB along with the active compound responsible for this mechanism.

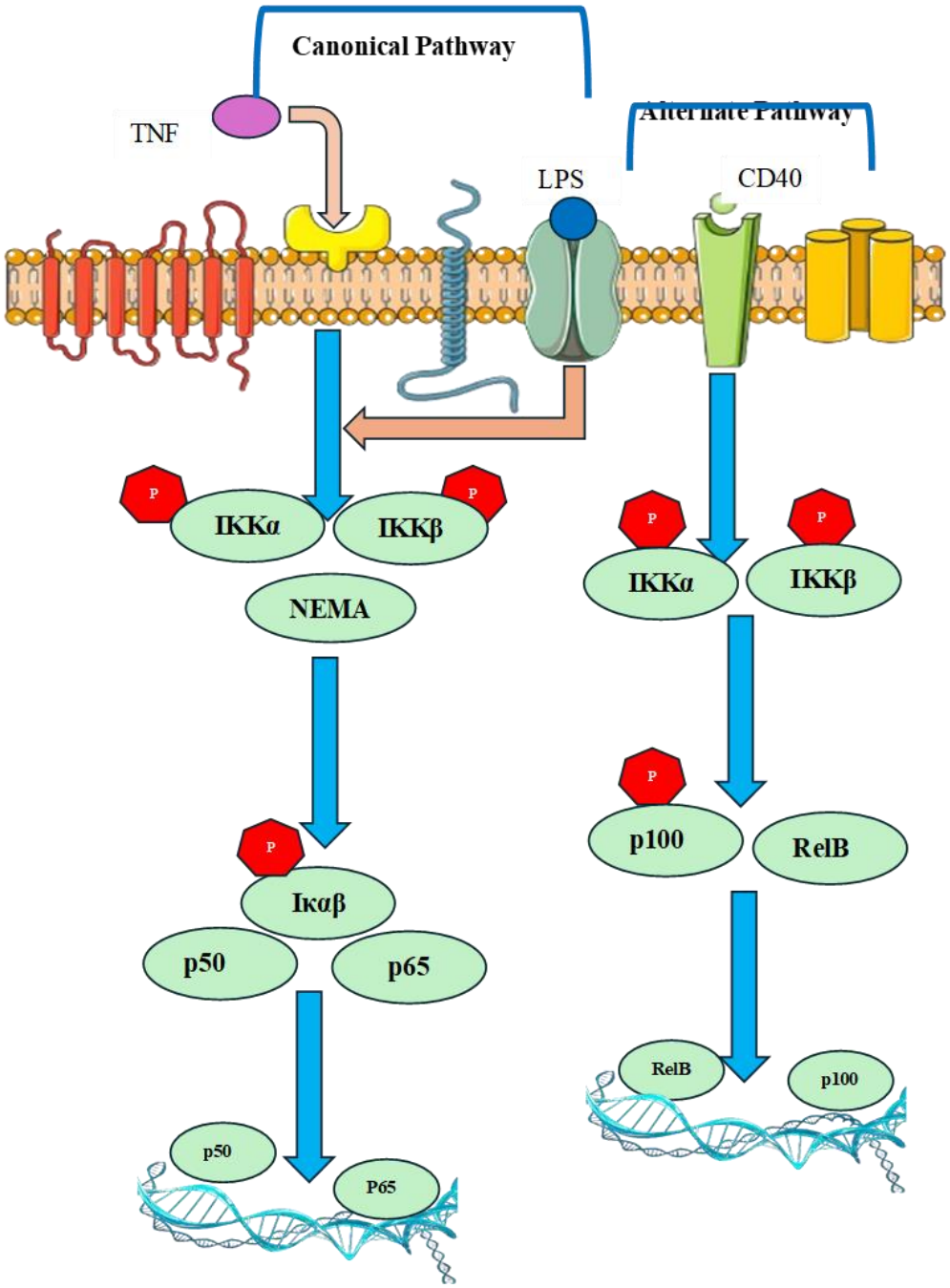

Fig. 2.2: NF-κB signal transduction pathway involve in inflammation

Table 1: Plants that modulate the NF-κB along with the active compound responsible for this mechanism.

Plant	Active Compound	Class of compound
Helminthostachys zeylanica	Neougonin A	Flavonoid
Patrinia scabra	Patriscabrin F	Iridoid
Forsythia koreana	Koreanaside A	Lignin
Tetrastigma hemsleyanum	S-(−)-trolline	Alkaloid
Psacalium decompositum	Cacalol acetate	Sesquiterpene

Targeting JAK-STAT with Phytomedicines

The Janus kinase/signal transduction and activator of transcription (JAK-STAT) is an important signaling pathway that plays a pivotal role in the pathogenesis of inflammatory diseases. Composed of five important members JAK1, JAK2, JAK3, and TYK2, the JAK family is expressed by different cross various cell types and plays a crucial role in cytokine signaling and other cellular processes. The binding of type I/II cytokines to their cognate receptors leads to oligomerization of the receptors, which in turn causes separation of the intracellular portion of receptors, resulting in the activation of receptor-associated JAKs and initiation of the JAK-STAT pathway. Phosphorylation of JAK takes place, serving as docking sites for STAT transcription factors. Phosphorylation of STAT causes conformational changes in inactive cytosolic STAT, resulting in the formation of active homodimers, heterodimers, or tetramers. These active sites then translocate in the nucleus, serving as a transcription factor for gene expression (Banerjee et al.,2017; Sarapultsev et al., 2023). Aberration in the JAK-STAT pathway can lead to oncogenic transformations and other life-threatening conditions. Several studies have proved the distinct roles in different inflammatory diseases (Coskun et al., 2013; Malemud, 2018).

Targeting the JAK-STAT pathway is one of the most important therapeutic options to treat inflammatory diseases. Studies have shown that the presence of unique compounds in plants can actively target the JAK-STAT pathway, providing an opportunity to treat life threatening inflammatory diseases. Fu et al., (2022), have successfully targeted the JAK/STAT signaling pathway to treat atherosclerotic inflammation by using Glycosides from *Buyang Huanwu Decoction*. Another study showed that the extract of *Paederia scandens* inhibits the phosphorylation of JAK 2 and STAT 3, regulating cell proliferation and reduce the mRNA LEVEL OF-IL-6, IL-b and IL-17 (Chen et al., 2022).

Neuroinflammation is one of the most common causes of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease (PD), multiple sclerosis (MS) amyotrophic lateral sclerosis (ALS), and other neurological disorders Studies have shown that the phenolic and alkaloid compounds from natural herbal products, including curcumin can be used to target JAK/STAT and other pathways to treat neurodegenerative disorders (Kooshki et al., 2023). Phytomedicines have also been used to manage skin inflammatory diseases, such as Atopic Dermatitis. Biomolecules, such as *Leonurine, Astragalin,* and *Diosmetin* prevent the release of cytokines and target the JAK/STAT pathway. Furthermore, these biomolecules also actively target the SOCS family of proteins, modulating the JAK/STAT mediated pathway in the pathogenesis of atopic dermatitis (Kopalli et al., 2022).

P13K/AKT/mTOR Pathway Modulation

The P13K-AKT-mTOR signaling pathway plays a pivotal role in various physiological conditions and the pathogenesis of inflammatory diseases. Several researchers have shown that the P-13-AKT-mTOR pathway is a major hub in external stimuli, including TLRs, IL-6, insulin, and EGF. P13K, a family of five lipid kinase members, has been reported in the transformation activity of the vital oncogenes and activation of protein-tyrosine kinase. AKT is another essential member of the P13K-AKT-mTOR signaling pathway that plays a vital role in protein synthesis, metabolism, cell cycle progression, and survival. AKT is involved in the immune cell activation and the release of pro-inflammatory cytokines by inhibiting the transcription factor NF-kB. The mammalian target of Rapamycin, also known as mTOR is an important component of mammalian cells that plays a key role in cell survival, growth, and the synthesis of essential nucleotides, and lipids. mTOR also causes the activation of neutrophils and enhances the release of proinflammatory cytokines (Roy et al., 2023).

Modulating the P13-AKT-mTOR signaling pathway is one the most important strategies for treating inflammatory diseases. Rapamycin, an inhibitor of mTOR, is most commonly used to treat atopic dermatitis (Yang et al., 2014). Similarly, several plant-based medicines have also been used to target the P13K-mTOR pathway for the treatment of inflammatory diseases associated with skin, nervous system, and cancers. For example, bioactive compounds from *Actinidia arguta* have been successfully targeting the P13K-AKT-mTOR pathway to treat glioblastoma and skin diseases (Bae at al., 2016; Macedo et al., 2023). The P13K/AKT/mTOR signaling pathway also plays an essential role in the pathogenesis of neurodegenerative disorders such as, Alzheimer's disease, Parkinson's disease and other inflammatory diseases associated with the nervous system. Natural plant-based products such as curcumin and Pueraria lobata can be used to treat different neurodegenerative disorders by directly targeting the P13K/AKT/mTOR signaling pathways. Similarly, active compounds, such as alkaloids, phytosteroid secondary metabolites, and ursolic acid, from phytomedicines can be used to inhibit the release of pro-inflammatory cytokines and modulating the pathway (Fakhri et al., 2021).

Atherosclerosis is one of the common chronic inflammatory diseases that affects large and medium-sized arteries, leading to ischemia, stroke, and other life-threatening diseases. Studies have shown the direct role of the mTOR signaling pathway in the pathogenesis of arthrosclerosis. Many natural compounds extracted from plants have shown their action against occurrence and development of atherosclerosis. For example, different polyphenols, alkaloids, and glycosides can be used to regulate blood lipids concentration, reduce inflammatory factors, and alleviate cellular senescence to lower the chances of arthrosclerosis occurrence (Wu et al., 2023).

Anti-inflammatory Compounds of Plant Origin

Plants have played a key role in treating inflammation for centuries. Application of the novel active compounds from plants and other natural sources for pharmaceutical purposes has been gradually increasing in recent years. Studies have shown the potential of unique active compounds against the release of cytokines and inhibition or modulation of the pro-inflammatory signaling pathways. Plant-derived medicines also interact with gut microbiota, leading to the release of the

release of low-molecular-mass products of secondary metabolisms. These metabolites are small in size with more bioavailability. Due to the production of secondary metabolites, phytomedicines are potential source of therapeutic agents to treat different life-threatening inflammatory diseases. The most common biomolecules present in phytomedicines include polyphenols, alkaloids, peptides, and several other novel compounds.

Polyphenols

Phenolic compounds are present in most of the phytomedicines and have anti-inflammatory, antioxidant, antibacterial, and anti-proliferation activities. Studies have shown that the application of phenol-rich plants can be used to treat chronic hepatitis, neurodegenerative diseases, arthritis, etc. Phenolic compounds interact with pro-inflammatory cytokines and module the inflammatory pathways. For instance, flavonoids, a class of phenolic compounds, inhibit the release of TNF-α and IL-6 from macrophages. Phenolic compounds, such as Hesperidin, luteolin, chrysin, naringin, and kaempferol, interact with the MAPK pathway to treat inflammation. Quercetin, a flavonoid, inhibits the PI3K/Akt signaling pathway and is used to treat malignancies. Curcumin is another important class of phenolic compounds that modulate the NF-κB. Fisetin, naringenin, and butene inhibit the MAPK signaling pathway, leading to dysregulation in LPS-induced inflammatory protein expression and cytokine production. The below table explains the major classes of phenolic compounds along with their mechanism of action against inflammation and the sources of their origin (Calixto et al., 2004; W. Liu et al., 2023).

Table 2: Phenolic compounds with anti-inflammatory properties, their targeted pathways, and plant sources.

Phenol Compound	Pathway Targeted	Plant source
Curcumin	Modulation of NF-κB	Turmeric (Curcuma longa)
Hesperidin	Alteration of MAPK signaling pathway	Citrus fruits
Kaempferol	COX inhibition and prevent release of iNOS	Broccoli, apples, and strawberries
Quercetin	Modulation of the PI3K/Akt signaling pathway	Onions, grapes, berries, cherries
Fisetin	Inhibit the MAPK signaling pathway	Euroasiansmoketree, Acacia berlandieri, and Acacia greggii
Naringenin	Inhibit the MAPK signaling pathway	Citrus fruits, bergamot, and tomatoes

Alkaloids

Alkaloids are unique nitrogen-containing organic compounds that can be commonly extracted from plants and fungi. Studies showed that there are almost 12,000 different classes of alkaloids. These alkaloids can be divided into organic amines, quinolines, isoquinolines, indoles, pyrrolidines, and piperidines. These secondary metabolites of medicinal plants possess unique anti-inflammatory properties, such as antioxidant, anti-inflammatory, and antimicrobial effects. Alkaloids modulate the release of cytokines and inhibit the activation of pro-inflammatory pathways to reduce inflammation. Caulerpin, indole alkaloids, can be extracted from Caulerpa racemose and possess anti-inflammatory properties by reducing the production of TNF-α, IFN-γ, IL-6, and IL-17. Furthermore, it also alters the NF-kB p65 and increases the production of IL-10. Other indole alkaloids include Cassiaindoline from *Cassia alata*, Strictosidine from *Uncaria rhynchophylla*, and Alstoyunines E from *Alstonia yunnanensis*. There are several other alkaloids with anti-inflammatory activities (Bai et al., 2021).

Carbazole alkaloids are another important class of alkaloids with anti-inflammatory potential.

O-Demethylmurrayanine from *Clausena lansium* attenuates the production of superoxide anions. Other Carbazole alkaloids alter the production of cytokines, suppress COX-2 enzyme, and modulate pro-inflammatory pathways (Bai et al., 2021).

7-Methoxy-1-propenoic is a novel β- β -carboline alkaloid isolated from the hairy root culture of *Eurycoma longifolia* and its anti-inflammatory mechanism was investigated. Studies have shown that this unique β-carboline reduces the NO, PGE2, and IL-6. Other sources of β-carboline include *Ailanthus altissima, Peganum harmala,* and *Houttuynia cordata*. Quinolone alkaloids are important anti-inflammatory alkaloids that inhibit NF-κB levels, alter COX-2 and 5-LOX activities, and reduce level of TNF-a, IL-6, PGE2, and NO (Souto et al., 2011; Bai et al., 2021).

Peptides

Plant-derived bioactive anti-inflammatory peptides are the most unique class of biomolecules that have been used to treat different inflammatory and neurodegenerative disorders, such as Rheumatoid arthritis, Alzheimer's disease, hepatitis, cardiovascular disease, and cancer. Millet bran peptides can be used to alter the JNK and p38 pathways. Similarly, rapeseed crude hydrolysate from rapeseeds has anti-oxidant potential and is used to treat inflammation by reducing the oxidant enzymes. Studies have shown that wheat peptides blocked the MAPK pathway downregulating the protein phosphorylation levels of ERK and p3. Several plant-derived peptides, such as rice bran, alter the s inhibited NF-κB signalling pathway by decreasing IκB protein phosphorylation. Several peptides also modulate the MAPK pathway by inhibiting the release of IL-1, IL-6, and TNF cytokines (Wanlu Liu et al., 2022).

Challenges and Opportunities Associated with Phytomedicines

Although phytomedicines are obtained from a "natural" source it is believed that these are safer than conventional drugs, the low solubility and poor bioavailability of the phytomedicines can lower the effectiveness of phytomedicines. Furthermore, a higher dose of some herbal medication can also cause nephropathies and urothelial malignancy as in the

case of *Aristolochia* spp. Studies have also shown that herbal medication can alter the pharmacokinetic profile of prescribed conventional pharmaceuticals and lead to complications such as allergies (Khan and Rauf, 2014). Another important issue in the application of phytomedicine is low purity control regulations, leading to adulteration and pollution of the available phytomedicines. Herbal medications rarely meet the requirement of standardization, which is partly due to a lack of scientific information about the operating pharmacological principles of the extracted phytocompounds, as well as the fact that the plants are not grown under controlled conditions.

To overcome the issues associated with the solubility and bioavailability of phytomedicines, drug-delivery technologies have attracted enormous attention in the recent era. Encapsulation of plant-derived biomolecules into nanoparticles provides an opportunity to enhance the drug bioavailability and sustained release of drug at active sites. A novel drug-delivery system can actively target the inflammation site and increase the therapeutic index of the drug. Furthermore, herbal medication is also an alternative to chemotherapeutic agents, providing an opportunity to overcome the drug resistance (Sajid et al., 2019).

Conclusion

Phytomedicines have been one of the most pivotal components of complementary medicines from centuries. Plants contain several unique biomolecules, such as polyphenols, peptides, and alkaloids, which modulate the inflammatory signal pathways and inhibit the release of cytokines from immune cells. Numerous studies, including in-vivo and in-vitro have been performed to uncover the potential of phytomedicines against inflammatory diseases. efficacy of herbal medicines. Thus, there is a need to focus on "green nano synthesis" to improve the bioavailability and sustained release of the drug. Furthermore, considering the side effects, contraindications, and pregnancy properties of plants is another major challenge that requires great caution before the application of phytomedicines. However, there is limited reliable evidence available on these matters. More evidence-based studies and meta-analyses could provide clearer guidance and approaches for healthcare professionals.

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