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Phytochemical Modulation of Inflammatory Biomarkers, Enzymatic Mediators and Molecular Signaling Pathway: A Comprehensive Review

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Abstract

Inflammation is characterized by a complex biological reaction caused by various harmful stimuli that are, for example, infectious agents, injuries, toxins, or oxidative stress. Although chronic inflammation is crucial for the protection and self-healing of the body from external attacks, there is no doubt that this phenomenon is also known to play the role of the triggering agent for the development of various diseases, such as rheumatoid arthritis, heart disorders, diabetes, inflammatory bowel disease, and even cancer. The processes mentioned above can be regulated by several mediators, such as cytokines, chemokines, prostaglandins, nitric oxide, and reactive oxygen species, through molecular mechanisms. The traditional anti-inflammatory drugs, for example NSAIDs and corticosteroids, are extremely effective; however, they cannot be used on a daily basis due to possible side effects. As a result, today plant medicine became quite common. Natural substances include a range of bioactive compounds like flavonoids, alkaloids, phenolics, terpenoids, and coumarins that have anti-inflammatory effects.

Keywords: Phytochemicals, Inflammation, Cytokines, NF-κB Pathway, MAPK Signaling, JAK/STAT Pathway, Cyclooxygenase (COX-2), Lipoxygenase (LOX), Oxidative Stress.

1 INTRODUCTION

Inflammation is one of the ways the body protects itself by developing a response to any foreign matter introduced into the body, such as microorganisms and any other form of irritants (Najmi et al., 2015). The symptoms of this disease include reddening, swelling, warmth, pain, and even inability to work.

Inflammation is initiated by the immune cells due to the activation of their pattern recognition receptors which trigger intracellular signaling reactions resulting in the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines increase vascular permeability, attract immune cells to the damaged sites and activate COX and LOX enzymes (Nikniaz et al., 2014).

However, due to the fact that the function of inflammation is to protect the body, its persistence leads to the development of chronic inflammatory conditions like arthritis, asthma, inflammatory bowel diseases, and cancer among others Hoggard et al., (2013).

That is why it is important to discover alternative therapies for the regulation of inflammation targets, especially natural ones.

Role of Oxidative Stress in Inflammation

It is important for the development and perpetuation of inflammation due to the generation of excessive ROS, which leads to oxidation. Oxidation happens whenever the generation of ROS is higher than the capacity of antioxidants in the body.

In the case of inflammation, the immune system produces an increased amount of ROS as an attempt to defend itself. Oxidative stress also elevates the activity of inflammatory mediators like NF-kB and MAPK; thus, it results in chronic inflammation.

Flavonoids and other plant compounds having an antioxidant effect help in reducing free radicals.

Role of Gut Microbiota in Inflammatory Disorders

Modern studies have shown that microflora is an essential component in the process of regulating immunity and inflammation reactions. There are many microbes in the human intestine that interact with the immune system in order to keep its balance.

Dysbiosis of the gut microflora has been associated with several inflammatory conditions, such as arthritis. The metabolites produced by the pathogens can activate the immune response, as well as result in elevated levels of pro-inflammatory cytokines.

Various natural compounds found in plants serve as prebiotics, fostering the development of friendly bacteria and balancing the intestinal flora, thereby reducing inflammation.

Inflammatory Biomarkers

The inflammatory markers are biological and chemical indicators that reflect the level of inflammation in the body. The cytokines such as TNF-α, IL-1β, and IL-6 play a critical role as mediators in the stimulation and exaggeration of the inflammatory response in table 1.

Immune cells are recruited to the site of injury by chemokines like MCP-1 and IL-8. Moreover, there are other proteins known as acute phase proteins like CRP which function as inflammatory markers (Padilla-Camberos et al., 2013).

Excessive production of the biomolecules like nitric oxide, ROS, and MMPs can lead to oxidative stress and tissue damage. The determination of these biomarkers is very important in disease progression and treatment success (Biedermann et al., 2013; Borghi et al., 2015).

Major Inflammatory Biomarkers

Table 1: Major Inflammatory Biomarker

Biomarker	Type	Function in Inflammation	Clinical Significance
TNF-α	Cytokine	Promotes inflammation, activates immune cells	Rheumatoid arthritis
IL-1β	Cytokine	Induces fever and inflammation	Chronic diseases
IL-6	Cytokine	Stimulates immune response	Infection
CRP	Acute protein	Marker of inflammation	Diagnostic marker
MCP-1	Chemokine	Recruits immune cells	Tissue injury

Inflammatory Enzymes

This is because these enzymes take part in the production of mediators that result in inflammation. These enzymes, which include cyclooxygenase enzymes, help in the formation of prostaglandins through arachidonic acid, causing pain and fever. Amongst these enzymes, COX-2 enzyme is highly inducible and associated with inflammation in table 2.

Lipoxygenases play an important role in the production of leukotrienes that enhance the permeability of the blood vessels and cause recruitment of immune cells. The process of inflammation leads to increased production of nitric oxide through iNOS (inducible nitric oxide synthase).

Phospholipase A2 is the enzyme which initiates the inflammatory process by releasing arachidonic acid from phospholipids of the membrane. Phytochemicals such as curcumin, gingerols, and boswellic acids have been found effective in inhibiting these enzymes (Ammon, 2006; Surh, 2003).

Table 2: Key Inflammatory Enzymes

Enzyme	Function	Role in Disease	Inhibition
COX-2	Prostaglandin synthesis	Pain & inflammation	Curcumin
LOX	Leukotriene synthesis	Asthma	Gingerol
iNOS	Nitric oxide production	Oxidative stress	Flavonoids
PLA2	Arachidonic acid release	Initiates inflammation	Terpenoids

Inflammatory Signaling Pathway

The inflammatory response is carefully controlled through signalling pathways in cells that regulate gene expression (Maheu et al., 2014). The first one is known as the NF-κB pathway, in which transcription of genes responsible for cytokines, adhesion molecules, and enzymes in inflammation is controlled (Figure 1).

The second important pathway is the MAPK pathway, which includes ERK, JNK, and p38 kinases. This group of proteins transmits external signalling and contributes to the formation of inflammatory mediators. Dysfunction of the MAPK pathway is associated with inflammatory disease.

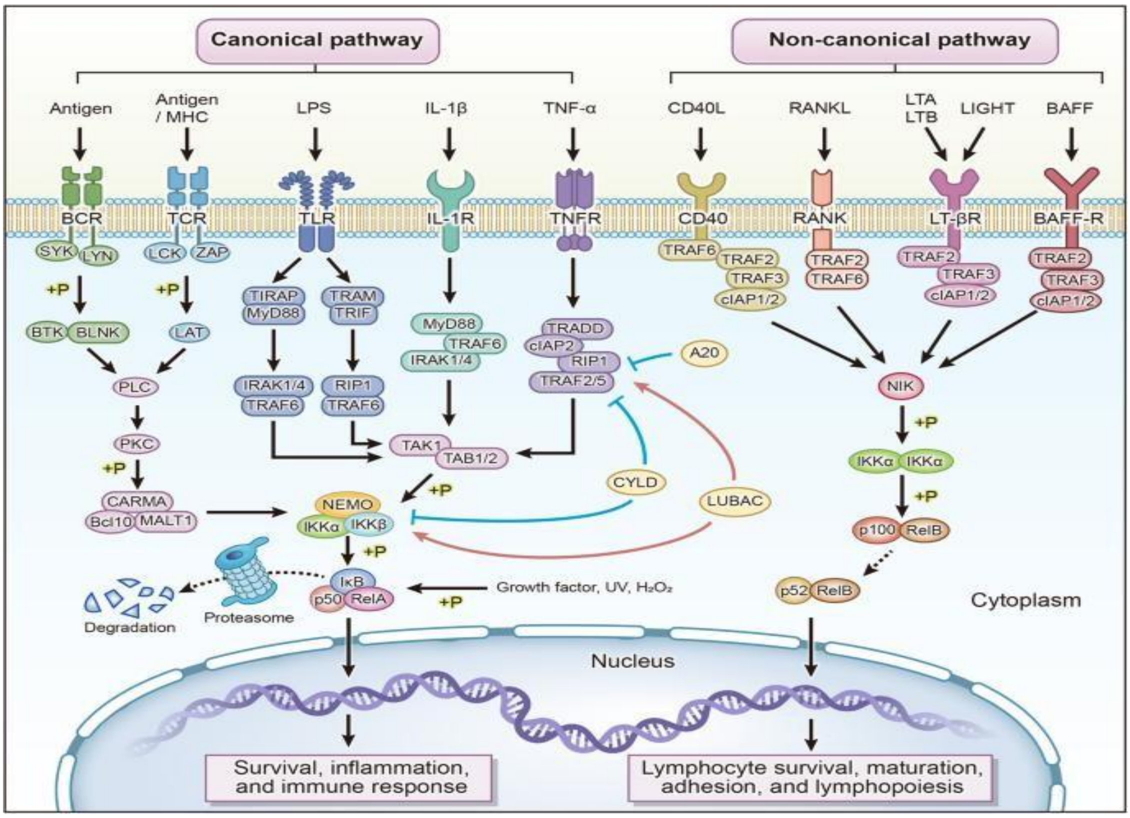

Figure 1: Inflammatory Signaling Pathway

JAK/STAT Signaling Pathway

JAK/STAT signaling pathway is an efficient mechanism of conveying information from cytokines and growth factors inside the cell nucleus. After cytokine binding occurs on the surface of the cell receptors, janus kinases (JAKs) get activated, and receptor phosphorylation takes place. This results in recruitment and activation of STAT proteins that subsequently dimerize and translocate to the nucleus, where they regulate gene expression. Prolonged JAK/STAT signaling pathway activation leads to development of chronic inflammation such as rheumatoid arthritis, psoriasis, and some types of cancer in figure 2.

Because of the critical involvement of the JAK/STAT pathway in inflammation, there have been attempts to utilise this pathway in the treatment of the diseases, and some phytochemicals have been identified as having the potential of influencing this signalling pathway (Asaduzzaman et al., 2026; Aggarwal & Shishodia, 2006).

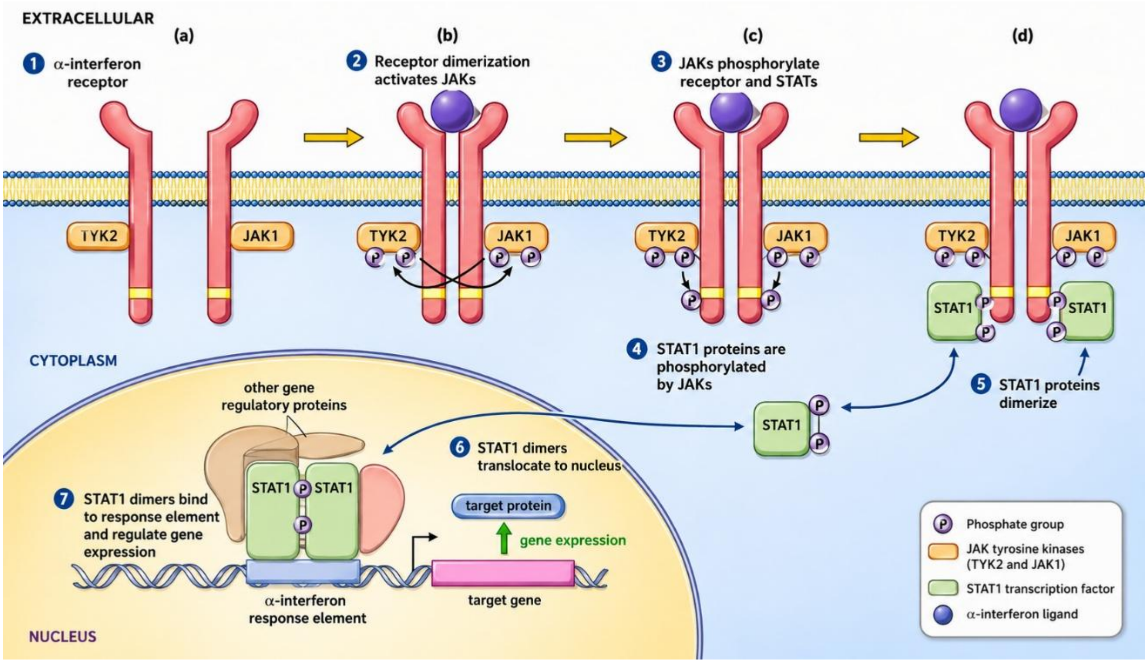

Figure 2: JAK–STAT Signaling Mechanism

2 MEDICINAL PLANTS WITH ANTI INFLAMMATORY ACTIVITY

Curcuma Longa (Turmeric)

The curcumin from the plant Curcuma longa is very popular because of its anti-inflammatory and antioxidant nature (Bagad et al., 2013). The reduction in the concentration of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 is seen due to the action of curcumin. Curcumin is also able to block the activity of NF-κB and decrease the activity of the COX-2 and iNOS enzymes. This leads to a reduction in the formation of prostaglandin and nitric oxide.

Zingiber Officinale (Ginger)

Gingerol, shogaol, and paradol are found in Zingiber officinale. The mentioned compounds all inhibit both cyclooxygenase and lipoxygenase pathways, hence reduced production of pro-inflammatory mediators like prostaglandins and leukotrienes. There are numerous studies demonstrating that the consumption of ginger leads to reduction in pro-inflammatory mediators such as CRP and TNF-α (Drozdov et al., 2012).

Rosmarinus Officinalis (Rosemary)

There are bioactive constituents found in Rosmarinus officinalis plants (Amaral et al., 2013). These are rosmarinic acid, carnosic acid, and carnosol. The bioactive constituents have strong antioxidative and anti-inflammatory effects since they can inhibit the activities of cytokines such as TNF-α and IL-1β (Mahluji et al., 2013; Rodrigues et al., 2012).

Borago Officinalis (Borage)

The plant Borage contains an omega-6 fatty acid known as Gamma Linoleic Acid (GLA) (Miceli et al., 2014). GLA functions through reducing the secretion of inflammatory substances and therefore has proven to be effective in the treatment of rheumatoid arthritis and inflammatory skin conditions.

Salvia Officinalis (Sage)

Phenolic components present in Salvia officinalis include rosmarinic acid and carnosol (Camargo et al., 2014; Bauer et al., 2012). The components prevent the formation of prostaglandins as well as regulation of inflammatory pathways such as NF-κB and MAPK (Shakibaei et al., 2012).

3 PHYTOCHEMICAL MODULATION OF INFLAMMATORY BIOMARKERS, ENZYMES, AND SIGNALING PATHWAYS

Phytochemicals block the production of pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin 1β, and interleukin 6. Phytochemicals are able to suppress the activity of chemokines and therefore limit the migration of immune cells. Phytochemicals also help in reducing oxidative stress biomarkers and acute-phase proteins in table 3.

Phytochemicals also inhibit the activities of several important inflammatory enzymes (Bishayee et al., 2013). several phytochemicals inhibit the activities of cox-2 as well as lox enzymes, resulting in reduced formation of prostaglandin and leukotriene molecules. inhibition of inos inhibits the synthesis of nitric oxide molecules.

Several important inflammatory signaling pathways are regulated by the activities of phytochemicals (Rahman et al., 2006). phytochemicals can inhibit the nf-κb pathway and thereby inhibit the inflammatory gene expression. in addition, the inhibition of the mapk signalling pathway reduces cellular stress response. some phytochemicals also modulate the jak/stat signalling pathway, regulating immune signalling. some phytochemicals activate the nrf2 pathway. Phytochemicals have demonstrated anti-inflammatory activities in clinical and experimental studies.

Table 3: Examples of Phytochemicals with Anti-Inflammatory Activity

Phytochemical	Class	Natural Source	Mechanism of Action	Target
Curcumin	Polyphenol	Curcuma longa (Turmeric)	Inhibits inflammatory enzymes and cytokines	COX-2, NF-κB
Quercetin	Flavonoid	Fruits & vegetables	Suppresses cytokine production	TNF-α, IL-6
Resveratrol	Phenolic compound	Grapes	Antioxidant and pathway modulation	Nrf2, NF-κB
Berberine	Alkaloid	Berberis species	Reduces nitric oxide production	iNOS
Gingerol	Phenolic compound	Zingiber officinale (Ginger)	Inhibits prostaglandin synthesis	COX, LOX
Boswellic acid	Terpenoid	Boswellia serrata	Inhibits leukotriene synthesis	LOX
Ellagic acid	Tannin	Pomegranate	Reduces oxidative stress	ROS

Recent Advances and Future Perspectives

Phytochemicals have a multi-targeting feature, which is important for targeting multiple biological targets to modulate the process of inflammation (Kolehmainen et al., 2012; Medzhitov, 2008).

The progress achieved in the field of molecular pharmacology and computational methods has significantly contributed to the knowledge of the natural anti-inflammatory molecules (Shin et al., 2020). Computational approaches such as molecular docking have helped in identifying phytochemicals that can interact with multiple biological targets, including COX-2, iNOS, and NF-κB.

Nanoparticles, liposomes, and phytosomes are emerging drug delivery systems that will improve the bioavailability of phytochemicals.

Further investigations should be focused on clinical studies, standardization of herbal formulation, and pharmacokinetics.

Challenges in Herbal Drug Development

In spite of some encouraging findings, there are various difficulties that are faced while creating phytochemicals as medicines. They are variation in composition of plants, absence of standardization, and paucity of clinical trials.

Moreover, other problems like low bioavailability and stability also have to be dealt with.

Progress in biotechnology and medicine will help overcome these barriers in the future.

4 FUTURE SCOPE OF PHYTOCHEMICALS IN PERSONALIZED MEDICINE

With the evolution of personalized medicine, there is an expectation that phytochemicals will be involved in such treatments in the future. This all comes down to how our bodies react to certain medications because of their genetic make-up. These three disciplines can be mixed together to produce a specialized anti-inflammatory drug.

5 CONCLUSION

Inflammation is a complicated biological phenomenon that requires the involvement of numerous mediators, enzymes, and signal transduction pathways. Their constant activation leads to the formation of many chronic diseases.

Plants can be considered a rich source of biologically active substances that can inhibit inflammatory reactions. Such phytochemicals as curcumin, flavonoids, and terpenoids can influence inflammation via the inhibition of mediators, modulation of signal pathways, and increased antioxidant defense.

The combination of ancient herbal knowledge with modern scientific methods may create a great chance for the creation of safe and efficient anti-inflammatory drugs. But more experiments and research should be done before this discovery can be used in practice.

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