Emerging Role of Phytochemicals in Immunomodulation and Metabolic Regulation: Mechanistic Insights and Therapeutic Potential

Ankita Balaso Patil, Snehal Tanaji Raut, Rahul Shivaji Adnaik

Department of Pharmacology, Anandi Pharmacy College,Kalambe Tarf Kale, Tal. .Karveer, Dist. Kolhapur, Maharashtra, India

Corresponding author: Ankita Balaso Patil
Email: ankitapatil9008@gmail.com
Doi: **10.5281/zenodo.17101332**
Received: 25 June 2025
Accepted: 05 July2025

ABSTRACT:
Immunometabolism, the expanding field of study at the nexus of immunology and metabolism, has become a major focus of biomedical research, providing insight into the complex interplay between metabolic pathways and immune cell activity. Numerous chronic illnesses, such as autoimmune diseases, infections, obesity, diabetes, and metabolic syndrome, are caused by immunological dysfunction and metabolic dysregulation. Phytochemicals are naturally occurring substances derived from plants that have garnered interest recently due to their anti-inflammatory, immunomodulatory, antioxidant, and metabolic-regulatory qualities. The mechanisms by which phytochemicals including flavonoids, alkaloids, terpenoids, and polyphenols affect important metabolic regulators (AMPK, mTOR, PPARs) and immunological signaling pathways (NF-κB, JAK/STAT, MAPK) are examined in this review. It also emphasizes how plant metabolites affect immunological homeostasis, mitochondrial function, and gut microbiome.
Preclinical and clinical evidence supporting their efficacy in managing autoimmune diseases and metabolic disorders is critically examined. Furthermore, the review discusses current challenges in the standardization, bioavailability, and clinical validation of phytochemicals, offering future perspectives on their integration into evidence-based therapeutic strategies. Phytochemicals, due to their multi-targeted actions and natural origin, hold promise as complementary or alternative agents in the treatment of complex immune-metabolic diseases.

Keywords: Phytochemicals, Immunometabolism, Autoimmune diseases, Metabolic syndrome, Natural therapeutics,

INTRODUCTION:

Importance of immune and metabolic homeostasis

Metabolism is a fundamental process essential to nearly all biological activities. Its integration with the immune system—referred to as immunometabolism—has become a leading area of research in immunology, driving major advancements in the field. It has been evident over the last ten years that metabolism is a key factor in controlling immune system activity in both health and illness. One important finding is that the metabolic condition of cells affects the Immune cell behavior and function [1]Moreover, the interaction between metabolic and immune pathways is vital for maintaining overall physiological balance [2].Recent developments in immunometabolism have revealed several important principles. Immune receptors and ambient metabolic cues, such nutrition, have a dynamic interaction that regulates responses.Bidirectional metabolic signaling, a technique that combines metabolic reprogramming and cellular signaling pathways, also influences the character of immune responses [3]. As seen in T cells, B cells, dendritic cells, and macrophages, this kind of

communication promotes immune cell activation, differentiation, and tissue-specific immunological activities. Furthermore, complex networks that affect cell signaling and interactions between cells and their surroundings are used by metabolism. The importance of intracellular and intercellular metabolic networks in immunometabolism is becoming more and more clear. The intricate interactions among dietary variables, fat tissue, and the immune system are one example of this [4].

Disorders related to immune dysfunction and metabolic dysregulation

When the immune system malfunctions, it unintentionally targets and assaults the body's own tissues, leading to autoimmune illnesses. A breakdown in immunological tolerance causes diseases like lupus, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease, which can lead to cause progressive tissue damage and ongoing inflammation.Standard treatments typically involve corticosteroids, immunosuppressive medications, and biologic agents; however, these therapies often carry substantial side effects and long-term health risks [5].Immunosenescence refers to age-related immune dysfunction, which increases older individuals' susceptibility to infections and potentially to autoimmune diseases [6]. This discussion emphasizes how age-related immune dysregulation contributes to vulnerability to infections. However, new research also points to a possible link between this immunological imbalance and a number of age-related conditions, including as osteoporosis, diabetes mellitus, Alzheimer's disease, and atherosclerosis.Obesity—characterized by excessive fat accumulation— has been closely associated with a number of health issues, including as diabetes, heart disease, high blood pressure, joint problems, and several types of cancer. The World Health Organization (WHO) reports that since 1975, the prevalence of obesity has tripled worldwide [7]. According to WHO estimates from 2016, over 1.9 billion persons were overweight, and over 650 million were obese [8]. It is concerning to note that the chance of dying young increases by roughly 31% for every 5-unit increase in body mass index (BMI) above 25 kg/m^2 [9].The metabolic syndrome, which is characterized by a number of disorders including high blood pressure (hypertension), abnormal lipid levels (dyslipidemia), and high blood sugar (dysglycemia), is largely caused by obesity. Cases of metabolic syndrome have increased as a result of the expanding obesity epidemic. In addition to this condition, being overweight or obese raises the chance of a number of other health problems, such as cardiovascular problems (such as hypertension), endocrine disorders (such as early puberty and polycystic ovarian syndrome), respiratory problems (e.g., shortness of breath, obstructive sleep apnea), and several cancers [10].Several studies [11–13] have demonstrated that metabolic syndrome considerably increases the risk of type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD). Compared to people without metabolic syndrome, those with the syndrome have a five-fold higher risk of type 2 diabetes and are at least twice as likely to develop ASCVD [14]. The human body is continuously exposed to many substances that cause free radicals, also known as reactive oxygen species (ROS), to develop. These unstable compounds give cellular structures unpaired electrons, which results in oxidative damage. Oxidative stress arises when the equilibrium between ROS and antioxidants is upset, and it plays a role in the emergence of several illnesses, including diabetes [15].

Elevated blood glucose levels are a hallmark of diabetes mellitus (DM), a complicated metabolic disease that is usually caused by either decreased insulin production by pancreatic β-cells or impaired insulin sensitivity, which impairs glucose uptake or energy generation [16]. Diabetes causes macrovascular problems, which involve large blood vessels and contribute to peripheral artery disease, coronary artery disease, and cerebrovascular disease, as well as microvascular problems, which affect small blood vessels in the kidneys (nephropathy), nerves (neuropathy), and eyes (retinopathy) [17].

The Rise of Phytochemicals in Natural and Complementary Medicine

In current years, nanotechnology has released exciting novel possibilities used for enhancing bioactivity of phytochemicals—naturally occurring plant compounds known for their significant therapeutic effects. Innovative approaches to medication administration, illness treatment, and nutritional enhancement have resulted from the combination of nanotechnology and phytochemicals. Making use of the special qualities of nanoparticles,Researchers have successfully addressed key limitations of phytochemicals, such as poor stability,

low solubility, and limited bioavailability, thereby unlocking their full potential for promoting human health [18].At the same time, metabolites originating from plants have drawn more interest due to their inherent capacity to alter immune responses.These bioactive compounds have significant anti-inflammatory, antioxidant, and immunoregulatory properties. They include flavonoids, alkaloids, terpenoids, and polyphenols. They affect important immunological signaling pathways, including mitogen-activated protein kinase (MAPK), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and nuclear factor kappa B (NF-κB). Furthermore, plant metabolites help to maintain the balance of the gut microbiota, which is essential for the stability of the immune system. This study explores the immunomodulatory functions of plant metabolites, looking at their modes of action and possible uses in the management of autoimmune disorders. Plant-based methods may present interesting supplementary or alternative techniques for addressing immune-related disorders as our understanding of their therapeutic effects grows [19].

This review purpose is to explore the therapeutic potencial of phytochemicals in modulating immune responses and regulating metabolic functions, with a particular focus on autoimmune and metabolic disorders. **The objectives** include:

- To explain the fundamental principles of immunometabolism.
- To discuss the mechanisms through which plant-derived metabolites influence immune and metabolic pathways.
- To highlight key phytochemicals with immunomodulatory and anti-inflammatory properties.
- To examine recent preclinical and clinical studies supporting the therapeutic use of phytochemicals.
- To identify the challenges and limitations in the clinical application of herbal compounds and suggest future research directions.

Immunomodulation and Metabolic Regulation: A Biological Overview

The immune system eliminates infections and keeps the body in balance, and metabolism is essential for immune system support[20]. The innate immune response is a fundamental defense mechanism present in all living organisms. It acts as a first line of protection against microbial pathogens, abnormal or foreign cells—such as tumor cells—and harmful substances released by dying cells. Effective immune function is essential for maintaining growth and metabolic balance. The innate immune system has a deep evolutionary origin, dating back to the earliest forms of life. However, when the immune system encounters unfamiliar antigens, it can become disrupted, potentially leading to the development of disease [21–23].

Immune System Basics

1. Innate vs. adaptive immunity

The distinction between innate (non-specific) and adaptive (specific) immunity has its roots in the early scientific debates between Paul Ehrlich and Ilya Metchnikoff, who argued over the relative importance of antibody-mediated versus cellular immune responses. This classification has been widely accepted for over a century [24]. However, recent advances in molecular and cellular immunology have challenged traditional views, blurring the lines between innate immunity—typically involving phagocytes and innate lymphoid cells (ILCs)—and adaptive immunity, which relies on lymphocytes. Emerging evidence suggests that innate immune cells can perform functions once thought to be exclusive to adaptive immunity as well as it plays a critical part in regulating all stages of responses of adaptive immunity .

2. Cytokines, macrophages, T-cells, etc.

Cytokine :

The "cytokine" generally refers to immunomodulatory substances like interleukins and interferons. However, there is ongoing debate among biochemists regarding which molecules should be classified as cytokines versus hormones. As scientific understanding deepens, the structural and anatomical distinctions between these two categories are becoming less clear. Traditional protein hormones typically circulate in the bloodstream at nanomolar concentrations [27, 28], with relatively stable levels. However, during situations like illness or trauma, some cytokines, like IL-6, can increase dramatically—by up to 1,000 times—despite being present in much lower (picomolar) [28–30] concentrations.

One key difference between hormones and cytokines may lie in their sources: while hormones are often produced by specific glands, cytokines are generated by a wide range of cells. Nearly all nucleated cells can produce cytokines, with epithelial and endothelial cells, along with resident macrophages, being significant IL-1, IL-6, and TNF-α producers [25, 26].

3. Immunometabolic Regulation of Macrophage Activation:

Over the past two decades, research has significantly advanced our understanding of the diverse phenotypes as well as functional roles for macrophages, highlighting their essential contributions to host defense, tissue homeostasis, and disease processes. More recently, metabolic research has revealed a close connection between changes in macrophage activity and phenotype and cellular metabolism [31]. The regulation of catabolic and anabolic pathways is fundamental, as these processes supply the energy and molecular building blocks required for cell growth and function. In-depth analysis of immunometabolic pathways has placed a spotlight on macrophages, which play pivotal roles in anti-inflammatory as well as pro-inflammatory responses also directly influenced by metabolic reprogramming. As our knowledge of the specific metabolic pathways and intermediates involved in immune responses continues to grow, it opens up promising opportunities for developing targeted immunometabolic therapies [32].

4. **T cells**

T cell development is carried out by the specialized organ known as the thymus. These cells develop from hematopoietic stem and progenitor cells found in the fetal liver or bone marrow, which go to the thymus to become T-cells.Although only a limited number of T-cell precursors every day, enter the thymus., they rapidly proliferate in response to the thymic environment and begins step differentiation of T-cell. During this development, they commit linkage of T-cell as well as initiate gene rearrangements of T-cell receptor (TCR), leading to the development of T cells with either αβTCR or γδTCR. Like a conductor directing an orchestra, the αβ T cells further differentiate into other subtypes, such as CD4 T cells, CD8 T cells, natural killer T (NKT) cells, and regulatory T (Treg) cells. Each of these subtypes is essential for coordinating and controlling immune system responses [33].

Metabolic Pathways

1. Role of AMPK

One important regulator that helps identify and preserve cellular energy balance is AMPK [34]. This serine/threonine protein kinase reacts to variations in the ratio of cellular AMP to ATP. AMPK affects both healthy and diseased processes in different tissues when it is active. Its activation increases the uptake of glucose in muscle tissue, inhibits the creation of fat cells and the generation of fat in the liver, and encourages the oxidation of fatty acids in the heart and liver [34, 35].

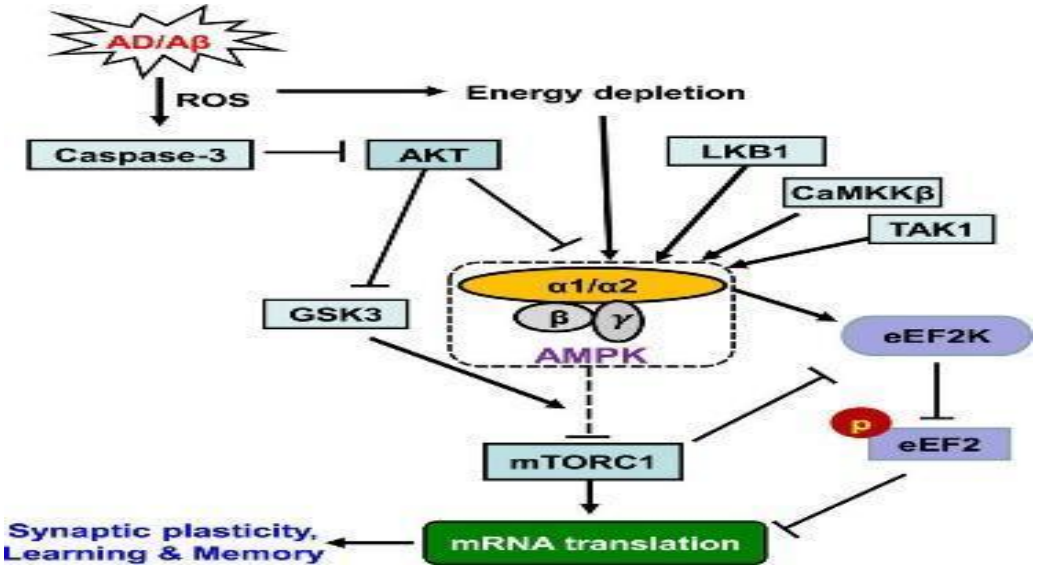


Figure 1: A model represents a AMPK Pathway

2. PPARs

Transcription factors known as peroxisome proliferator-activated receptors (PPARs) are essential for controlling a variety of physiological and pathological processes, including as cell division, morphogenesis, growth, and homeostasis [36]. The nuclear hormone receptor superfamily's members, these receptors, were first discovered in the 1990s as nuclear receptors that promote the proliferation of peroxisomes inside cells [36–38]. PPARα, PPARβ/δ, and PPARγ are the three PPAR isoforms, and each has a unique tissue distributions as well as specific functional roles [39].

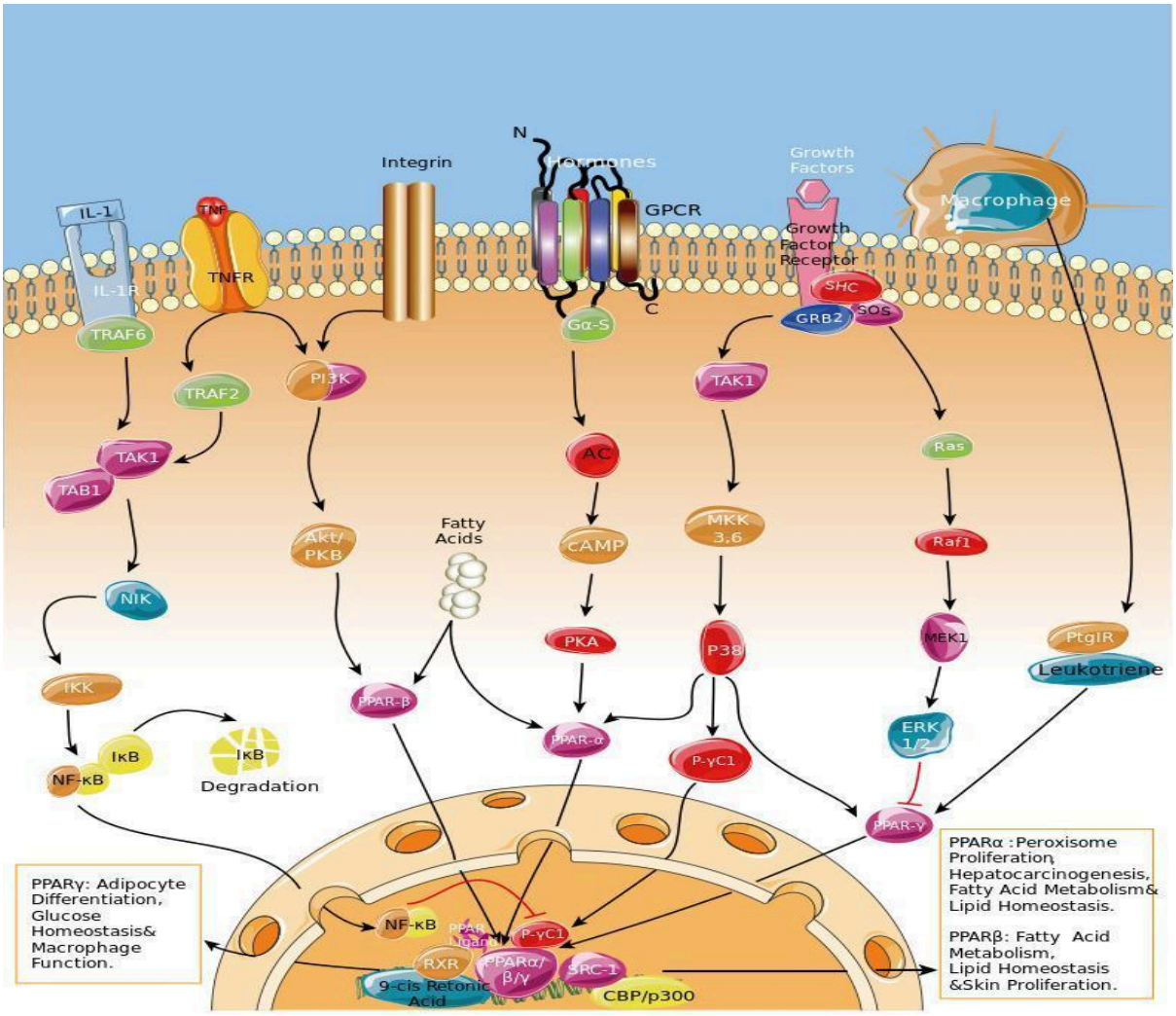


Figure 2:- A model represent a PPAR Pathway

3. mTOR:

The product of the TOR1 and TOR2 genes, whose mutations result in resistance against rapamycin-induced growth inhibition, was first discovered to be the target of rapamycin (TOR) in Saccharomyces cerevisiae [40]. Mammalian TOR (mTOR), also known as FRAP, RAFT1, or RAPT, is the mammalian analog of the highly conserved big protein TOR. The 2,549 amino acid protein that the human mTOR gene encodes shares 42% and 45% of its sequence with yeast TOR1 and TOR2, respectively. The ATM, ATR, and DNA-PK kinases are members of the phosphatidylinositol 3-kinase (PI3K)-related kinase family, which is closely connected to the kinase domain found around the C-terminus of mTOR. mTOR acts as a serine/threonine protein kinase in spite of these similarities [41].

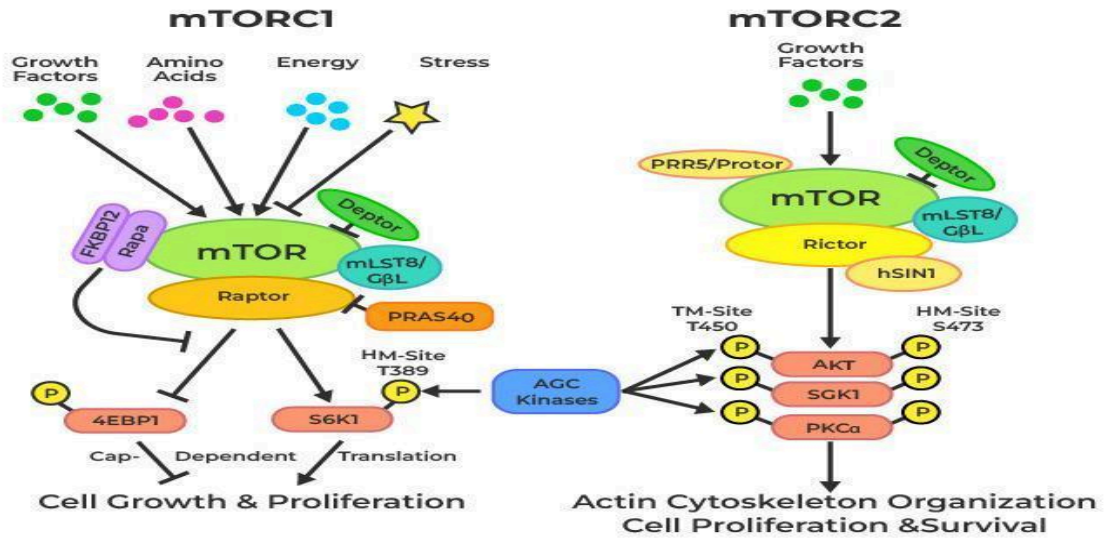


Figure 3:- A model represent a mTOR Pathway

4. Insulin signalling:

The intracellular cascade known as the insulin signaling system is essential for controlling the body's growth, metabolism, and survival. Insulin and insulin-like growth factors (IGFs) attach to their corresponding receptors to initiate this pathway, receptor of insulin (IR) and IGF receptors. Following this, the insulin receptor interacts with several Growth factor receptor-bound protein 2 (GRB2), insulin receptor substrate (IRS), Src homology 2 domain-containing protein (SHC), SH2B adapter protein 2/adapter protein with PH and SH2 domains (SH2B2/APS), and Growth factor receptor-bound protein 10 (GRB10) are examples of direct substrates. Numerous cellular signaling pathways involved in mitogenesis and metabolic control are triggered by these interactions. A succinct synopsis of each stage in the insulin signaling pathway is what this review attempts to provide [42–43].

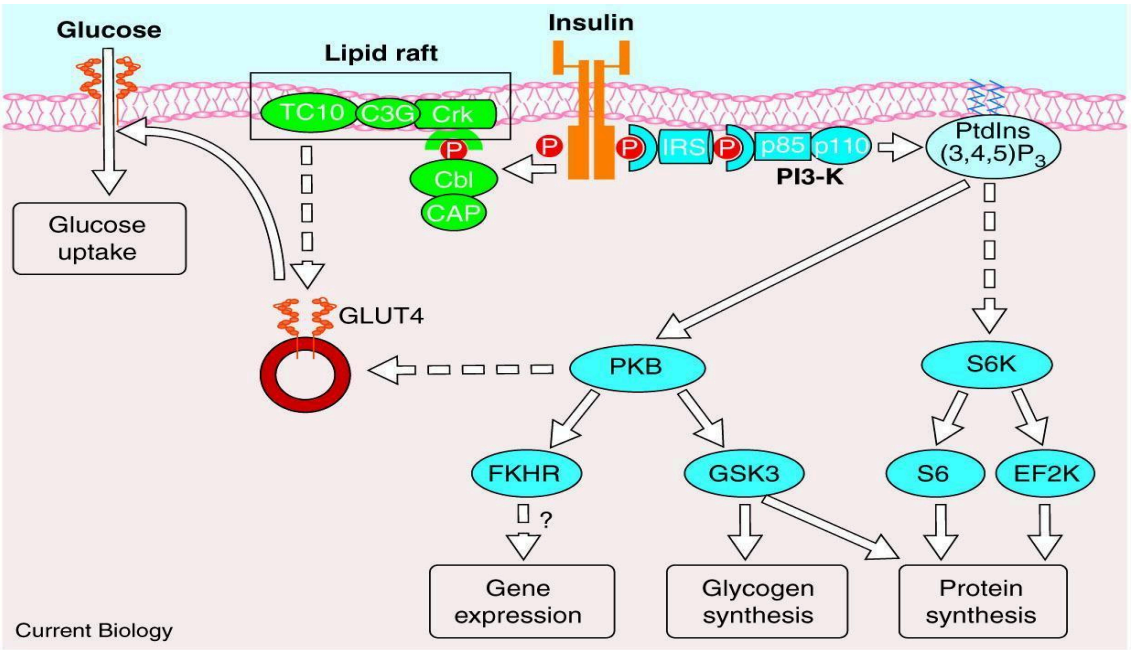


Figure 4:- A model describing the insulin signaling pathway (44)

Interrelationship between metabolism and immune function (immune metabolism)

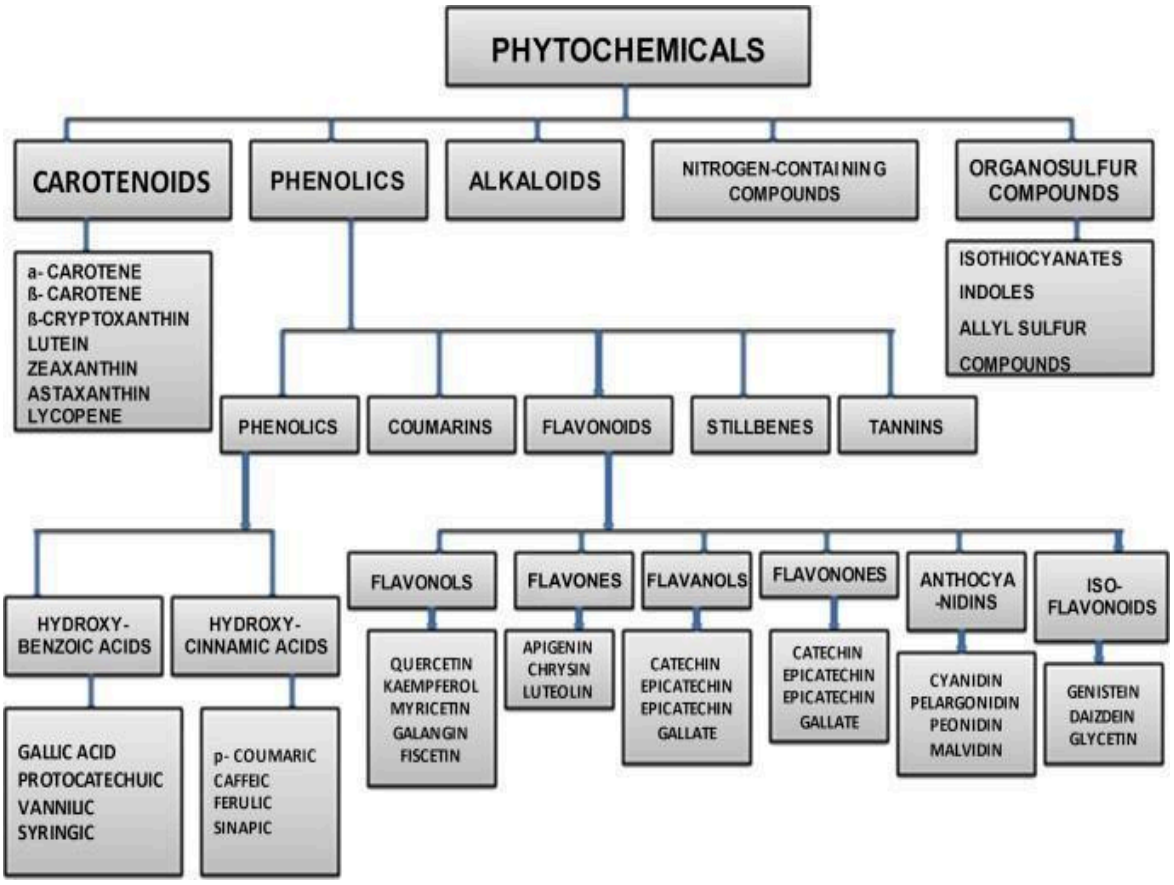
Metabolism broadly refers to the totality of biochemical reactions within an organism that either generate or consume energy, thereby supporting the maintenance of life. It encompasses all anabolic and catabolic processes occurring at both cellular and systemic levels [45]. Over the past twenty years, immunometabolism has emerged as a rapidly growing field with significant implications for biomedicine. Immunometabolism explores the intersection between the immune system and metabolic processes [46,47]. This field of research is founded on the knowledge that immune cells' metabolism of nutrients and energy varies significantly when they are activated as opposed to when they are at rest.Early research in immunometabolism primarily focused on characterizing the broad metabolic shifts that take place during immune cell activation [48–50].

Classification of Phytochemicals:

Phytochemicals are broadly categorized based on their chemical structure and biological activities. Major classes include:

Class	Examples	Biological Activities
Flavonoids	Quercetin, Catechins, Apigenin	Antioxidant, anti-inflammatory, immune modulation
Alkaloids	Berberine, Piperine	Anti-microbial, metabolic regulation
Terpenoids	Limonene, Ginsenosides	Anti-cancer, anti-inflammatory
Polyphenols	Resveratrol, Curcumin	Antioxidant, cytokine regulation
Saponins	Astragaloside, Ginsenosides	Immunostimulation, gut health
Tannins	Ellagitannin, Tannic acid	Antioxidant, antimicrobial

These compounds act through multiple molecular pathways, including modulation of NF-κB, MAPK, and JAK-STAT signaling, as well as interaction with gut microbiota.



Mechanisms of Immunomodulation by Phytochemicals

Plant metabolites influence immune function through multiple mechanisms that regulate the responses of innate as well as adaptive immunity. One important method is the suppression of proinflammatory signaling pathways, such as mitogen-activated protein kinase (MAPK), Janus kinase/signal transducers and activators of transcription (JAK/STAT), and nuclear factor kappa B (NF-κB). Numerous substances produced from plants, including flavonoids and polyphenols, inhibit the activation of NF-κB, which results in a reduction in the production of pro-inflammatory cytokines that are essential to the pathophysiology of autoimmune diseases, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). Another important mechanism involves boosting regulatory T cell (Treg) function while inhibiting autoreactive T cells. Substances like curcumin, quercetin, and resveratrol enhance Treg differentiation and activity, helping to avoid overreactions and preserve immunological tolerance against self-tissues. Furthermore, certain plant metabolites modulate B cell activity, lowering the production of autoantibodies that contribute to tissue damage in autoimmune conditions [51].

1. Modulation of Cytokine Production:

The term "cytokine" refers to immunomodulatory mediators for example interferons as well as interleukins. HoweverBiochemists argue on which compounds ought to be classified as hormones versus cytokines. As research advances, the anatomical and structural differences between the two categories are becoming less distinct. Nanomolar concentrations of conventional protein hormones usually fluctuate by less than an order of magnitude. Hematopoietic growth factors and other regulatory cytokines are produced by various cell types, in contrast to these traditional hormones, which are produced at specific locations across various body locations, either continuously or in response to stimulation. This broad distribution of cytokine production likely reflects their diverse regulatory functions [52].

Regulation of immune cell function:

Anti-inflammatory effect:

Inflammation is a procedure where different immune cells populations and related biological components work together to eliminate harmful substances or stimuli, such as damaged or infected tissues, pathogens, and toxic compounds [55-57]. Macrophages play a central role in directing both local and systemic inflammatory responses through their diverse functions, including antigen presentation, phagocytosis, and immunomodulation [58-59]. These functions are regulated in a finely tuned manner by multiple intracellular signaling pathways—such as NF-κB, AP-1, and STAT-1—which control the secretion of relevant cytokines and growth factors like interleukins, tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β) [57,60]. While most research has focused on the physiological and pathological roles of these protein molecules and their function as mediators between intracellular and extracellular immune regulation, recent in vitro and in vivo studies suggest that proteins alone may not fully explain macrophage-driven inflammatory responses. This has highlighted the potential involvement of other cellular components, including metabolites [61-63].

During pathogen-induced macrophage polarization, macrophage metabolism undergoes rapid rewiring towards aerobic glycolysis—a phenomenon known as the “Warburg effect.” This shift involves increased glucose uptake, enhanced glycolytic flux, conversion of pyruvate to lactate, and reduced oxygen consumption even in oxygen-rich conditions, enabling energy production while preserving carbon molecules essential for rapid cell proliferation [64-66].

Antioxidant effects:

Curcumin's antioxidant and free radical scavenging properties are widely known. Its unique chemical makeup, which consists of a β-diketo group, carbon–carbon double bonds, and phenyl rings with hydroxyl and methoxy groups-contributes significantly to its antioxidant activity [67,68]. Researchers attribute curcumin’s strong

antioxidant properties mainly because it can transfer hydrogen atoms from the phenolic group [69]. Over the past few years, there has been an increase in interest in exploring curcumin's free radical scavenging capacity, with studies demonstrating its effective neutralization of free radicals [69, 70]. Furthermore, proof recommends that curcumin have a essential role in scavenging radicals during lipid peroxidation processes. Curcumin helps shield cell membranes from oxidative damage by preventing lipid peroxidation, most likely by incorporating itself into the membrane structure[67, 68].Research also indicates that curcumin's inhibition of peroxidation is largely due to its ability to bind iron [69]. Additionally, curcumin is considered a promising antioxidant against the generation of hydrogen peroxide and superoxide radicals [69].

Regulation of Immune Cell Activity:

Plant metabolites are essential for modulating immune cell functions, especially affecting B cells, macrophages, and T cells—key players in autoimmune diseases. T cells, central to adaptive immunity, include subtypes like T helper cells (Th1, Th2, Th17) that drive inflammation, while regulatory T cells (Tregs) suppress excessive immune activity. Compounds derived from plants such as curcumin, quercetin, and resveratrol enhance Treg activity, thereby reducing autoimmunity and promoting immune tolerance. These metabolites also inhibit Th1 and Th17 cell activity, restricting the generation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), which are implicated in autoimmune conditions like rheumatoid arthritis and multiple sclerosis.

B cells, responsible for antibody production, can contribute to autoimmunity by generating autoantibodies that attack the tissues within the body. Certain polyphenols and flavonoids have been shown to control B cell activity by reducing the generation of autoantibodies and suppressing overactive immune responses.

Macrophages, crucial the innate immune system's constituent parts, exist in two phenotypes: M1 and M2 are pro- and anti-inflammatory, respectively.In autoimmune disorders, M1 macrophages sustain chronic inflammation by releasing cytokines that promote inflammation, while M2 macrophages aid in tissue repair as well as immune regulation. Plant metabolites such as epigallocatechin gallate (EGCG) from green tea and ginsenosides from ginseng encourage the transition from M1 to M2 macrophages, thereby reducing inflammation and promoting immune balance. By these mechanisms, plant-derived compounds help restore immune homeostasis, positioning them as promising therapeutic agents for managing autoimmune diseases with potentially fewer side effects compared to conventional immunosuppressive treatments [71].

Impact of Plant Metabolites on Gut Microbiota and Immune Homeostasis:
Immune homeostasis depends on the gut microbiota, and dysbiosis, or disruption of this microbiome, has been directly linked to the development and course of autoimmune disorders. Plant metabolites such as polyphenols, flavonoids, alkaloids, as well as dietary fibers can modulate the composition of gut microbes, thereby influencing immune responses and reducing inflammation. Compounds like curcumin, resveratrol, and catechins from green tea encourage the development of advantageous microorganisms, including Lactobacillus as well as Bifidobacterium, while repressing detrimental microbes linked to inflammation. These beneficial bacteria produce Butyrate, propionate, and acetate are examples of short-chain fatty acids (SCFAs) that support the integrity of the intestinal barrier and prevent the synthesis of proinflammatory cytokines[72].

Plant-derived Prebiotics like fructo-oligosaccharides and inulin serve as nutrients for these beneficial microbes, further enhancing their growth and activity. By strengthening the gut barrier, plant metabolites help prevent the leakage of harmful bacterial endotoxins (lipopolysaccharides) into the bloodstream—a phenomenon sometimes called "leaky gut syndrome" and implicated in autoimmune diseases. This barrier reinforcement reduces systemic inflammation and prevents overactivation of the immune system.

Additionally, proinflammatory T cells (Th1, Th17) and anti-inflammatory regulatory T cells (Tregs) are balanced by the effects of bioactive chemicals derived from plants on immune cells in the gut-associated lymphoid tissue (GALT). Maintaining this balance is critical to avoiding excessive immune activation and

mitigating autoimmune flare-ups. Due to their capacity to restore gut microbial equilibrium and promote immune tolerance, plant metabolites hold promise as therapeutic agents for autoimmune disorders. Future research should aim to identify specific plant compounds tailored to individual microbiome profiles for personalized treatment strategies [73].

Role of Phytochemicals in metabolite regulation:

Diabetes mellitus is a major global health concern marked by chronic diabetes mellitus that contribute for increased morbidity, mortality, as well as reduced life quality [74]. Persistent hyperglycemia causes vascular complications through mechanisms involving glucose toxicity and oxidative stress [75]. Effectively managing blood sugar levels is crucial to preventing these diabetic complications [76]. Key factors influencing post-meal blood sugar fluctuations include the availability of insulin, tissue insulin sensitivity, and the rate of intestinal digestion and absorption [77]. Drugs that address both oxidative stress and these anomalies could offer significant benefits for diabetes management. To improve glycemic control, current treatments include insulin and a variety of oral medications, including gliptins, biguanides, sulfonylureas, and alpha-glucosidase inhibitors. These medications can be used either alone or in combination [76]. However, these treatments frequently have adverse effects [78], making it challenging to manage diabetes without adverse effects. Consequently, there is ongoing interest in discovering safer and more effective natural therapies. Traditional medicine, commonly used even In the city areas as a substitute for traditional medical care approach, often involves multi-component extracts and intricate herbal mixes [79]. The combined impacts of the multiple constituents in herbal medicines are particularly advantageous for multifactorial diseases like diabetes [80].

The expansion and division of preexisting mitochondria is referred to as mitochondrial biogenesis. An α-proteobacteria endosymbiont that integrated into a host cell gave rise to mitochondria. Because of their bacterial heritage, mitochondria are able to replicate on their own and have their own DNA. Both nuclear and mitochondrial DNA encode mitochondrial proteins. Thirteen subunits of electron transport chain complexes I, III, IV, and V are encoded by 37 genes found in the circular, double-stranded, 16.5 kb mitochondrial genome (mtDNA). Furthermore, two ribosomal RNAs (rRNAs) and 22 transfer RNAs (tRNAs), which are necessary for translating respiratory subunit mRNAs inside the mitochondrial matrix, are encoded by mtDNA. Coordinated synthesis and import of roughly 1000–1500 nuclear-encoded proteins, which are made by cytosolic ribosomes, are necessary for proper mitochondrial biogenesis [81]. Coordination of mtDNA replication, mitochondrial fusion, and fission processes is also essential [82]. Environmental Mitochondrial biogenesis is influenced by a number of circumstances, including exercise, calorie restriction, cold exposure, oxidative stress, cell division, renewal, and differentiation. Changes in the number, size, and mass of mitochondria are all part of this process.

Preclinical Evidence:

Phytochemicals are initially tested *in vitro*, followed by *in vivo* studies using animal models, and ultimately in human trials. Choosing the appropriate experimental model is crucial to minimize bias and errors. This study focused on evaluating phytochemicals that reduce inflammation in vivo and in vitro, and exploring plant-based candidates for anti-inflammatory drugs. In this section, we discuss potential phytochemicals that have been investigated in preclinical studies for their effects on inflammatory diseases and related complications.

Clinical Studies:

Several clinical studies have explored the immunomodulatory potential of polysaccharides, with Astragalus membranaceusβ-glucan and Echinacea purpurea are the ones that are being studied the most. In a clinical study conducted by Jiang et al. [88], dialysis fluid containing Astragalus extract (20 mL/2 L) was administered for one week to 28 stable patients receiving continuous ambulatory peritoneal dialysis. In comparison to pre-treatment levels, the treatment led to higher levels of nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α), as well as increased macrophage phagocytic activity. Furthermore, Ji et al.[89] evaluated 128 patients with colorectal cancer to determine the impact of preoperative Astragalus treatment. The results showed increased post-operative natural killer (NK) cell activity. Another study investigated Astragalus's immunomodulatory effects in 72 patients experiencing acute exacerbations of bronchial asthma [90]. The findings showed that by

increasing T lymphocyte and NK cell immunological activity, a 14-day combination of conventional therapy with Astragalus injections greatly enhanced treatment outcomes.

Challenges and Limitations:

Current Challenges in Autoimmune Disease Treatment

Because of the continuous course of autoimmune illnesses and the complex immune system malfunction, managing these conditions continues to be extremely difficult. The main goals of current therapies, which include immunosuppressants, biologic medicines, and corticosteroids, are to lessen inflammation and suppress the overreactive immune response. But these therapies often fail to target the underlying cause of autoimmunity and are associated with significant long-term side effects, such as heightened infection risk, organ toxicity, and metabolic complications. Furthermore, the high cost of biologic drugs limits their accessibility, especially in resource-limited regions. Another key difficulty lies in the variability of disease symptoms and individual responses to treatment, which hinders the development of personalized therapeutic strategies. Despite continuous therapy, many patients still face the risks of relapse and disease progression. In light of these limitations, there is increasing interest in safer, more cost-effective alternatives—such as plant-derived metabolites—that exhibit immunomodulatory properties with fewer adverse effects [91].

Need for Standardization and Quality Control in Herbal Medicine:

In order to guarantee their safety, efficacy, and consistency, stringent standardization and quality control are desperately needed, as seen by the growing interest in plant-based treatments for autoimmune disorders. Due to variations in plant species, cultivation conditions, harvesting practices, processing methods, and storage, herbal medicines frequently exhibit variability in composition, potency, and bioavailability in contrast to conventional pharmaceutical drugs, which are subject to stringent clinical testing and regulatory scrutiny. The concentration of bioactive components in herbal products can be significantly impacted by extraction techniques as well as environmental factors including soil quality and climate. Furthermore, if not properly managed, the danger of contamination with heavy metals, adulterants, or microbial toxins poses serious health risks [92].

To address these issues, the implementation of standardized procedures—including phytochemical profiling, functional bioassays, and advanced analytical instruments such as nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectrometry (GC-MS), and high-performance liquid chromatography (HPLC)—is essential. Regulatory bodies must enforce stringent quality assurance measures to ensure that plant-based formulations consistently deliver therapeutic benefits. Furthermore, the clinical effectiveness of these therapies should be validated through well-structured randomized controlled trials (RCTs) to confirm their immunomodulatory potential in autoimmune disease treatment. Enhancing global regulatory standards and adherence to Good Manufacturing Practices (GMPs) will facilitate Herbal remedies' incorporation into conventional medicine, ensuring their safe as well as reliable use as complementary or alternative treatment options [93].

Conclusion:

Phytochemicals represent a promising class of natural bioactive compounds with potential for immunomodulatory and metabolic regulation. Their ability to target key immune signaling pathways, reduce inflammation, balance gut microbiota, and regulate metabolic enzymes positions them as attractive candidates for managing chronic conditions like autoimmune diseases and diabetes.

However, their clinical translation is hindered by challenges in standardization, bioavailability, and regulatory oversight. Advanced formulation techniques, such as nanotechnology-based delivery systems, and rigorous clinical studies are essential to realize their full therapeutic potential. With growing scientific interest and technological advancements, phytochemicals could soon emerge as integral components of mainstream therapeutic strategies.

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