CHAPTER 18

Anti-Inflammatory and Immunomodulatory Properties of Natural Products

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ABSTRACT: Inflammation and immune system activation are central body pathways that work in concert as a vital defense mechanism against harmful stimuli like pathogens, damaged cells, and toxic compounds. They are essential for maintaining health and initiating the healing process. However, prolonged inflammation and immune system activation are indeed dangerous, as it can damage healthy cells and tissues and are linked to numerous chronic diseases. Natural compounds are promising agents that exhibit inflammation and immunomodulatory properties. Natural products have been extensively applied against various inflammatory and immune system disorders, i.e., rheumatoid arthritis, inflammatory bowel diseases, and plague psoriasis. The current chapter discusses the importance of different natural products (flavonoids, alkaloids, terpenes and terpenoids, curcumin, and andrographolide) in the regulation of inflammatory and immune system response. Moreover, the different pathways that are targeted by natural products against these disorders are also discussed in this chapter. Furthermore, this chapter emphasizes future research on the safety and effectiveness of natural products against these inflammatory and immune system disorders.

The tumor promoting role of chronic inflammation makes it a viable therapeutic and preventive target. Unlike acute inflammation, a transient and protective mechanism arises from unresolved stimuli i.e. persistent pathogens, autoantigens or cellular stress which ultimately cause tissue damage via cytokine overproduction. This process underlies cardio-vascular diseases (endothelial dysfunction), cancer (genome instability) and Alzheimer's (microglial activation), positioning immune modulation as a key therapeutic strategy. Sepsis is a life-threatening response caused by dysregulated immune response to infections, leading to acute organ dysfunction (Singh et al., 2019).

When homeostasis fails due to persistent triggers (e.g., autoimmunity, metabolic disorder), protective immune responses become pathogenic. Sustained cytokine release (e.g., TNF- α, IL-6) promotes tissue damage, while immune cells exhaustion leads to immunosuppression, a paradox seen in cancer, autoimmune diseases and neurodegeneration. For instance, in rheumatoid arthritis, autoantibodies drive synovitis in diabetes, and adipose tissue inflammation exacerbates insulin resistance. Targeting these pathways with natural immunomodulators may restore balance (Cao et al., 2023).

Non-steroidal anti-inflammatory drugs are first-line treatments for inflammation and pain. They work by inhibiting cyclooxygenase (COX) enzymes, reducing prostanoid production. Classic NSAIDs (e.g. indomethacin) non selectively block COX-1 and COX-2 while COX-2 inhibition

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alleviates inflammation, COX-1 suppression causes gastrointestinal ulcer and renal toxicity. Long term use also increases cardiovascular risks. Unlike immunomodulation, NSAIDs fail to address underlying immune dysregulation in chronic diseases (e.g. rheumatoid arthritis) highlighting the need for safer alternative like natural multi target compounds (Narsinghani & Sharma, 2014).

Natural products that are sourced from terrestrial and marine organisms found an invaluable repository of bioactive metabolic compounds that contribute to multiple pharmacological companies. Paclitaxel and curcumin are some important natural compounds that play an important role in the regulation of cancer and antibiotic resistance (Wei et al., 2017). Unlike one-target artificial drugs, natural drugs often exhibit polypharmacology for their anti-inflammatory and immunomodulatory properties (Ahmad et al., 2025). The current chapter discusses in detail the anti-inflammatory and immunomodulatory properties of natural compounds.

INFLAMMATION AND IMMUNE SYSTEM BASICS

Chronic inflammation underlies diseases such as inflammatory bowel diseases, autoimmune disorders and certain types of cancers. It is categorized as either acute or chronic that leads to fibrosis, angiogenesis and tissue damage. Chronic inflammation, originating from extrinsic sources (such as infections) or intrinsic mutations, drives tumorigenesis and immunosuppression. Immune cells like macrophages and T-cells sustain this process via cytokines (TNF- α, IL-6) and oxidative stress pathways that are targeted by natural anti-inflammatory compounds (Sohrab et al., 2023).

The inflammatory response involves coordinated activation of signaling pathways regulating proand anti-inflammatory mediators. TNF-α represents the archetypal proinflammatory cytokine, rapidly released upon injury. NF-κB activated by TNF-α and IL-1, regulates expression of inflammatory genes. COX-2 produces inflammation-sustaining prostaglandins. These pathways form an interconnected network: TNF-α activates NF-κB, which upregulates COX-2 and IL-6, forming an inflammatory cascade. Natural products often target multiple nodes of this network simultaneously (Al Bander et al., 2020; Ghafoor et al., 2024). Immunomodulation is defined as the therapeutic regulation of the immune response. It is increasingly targeted by using natural compounds. Mushroom-derived polysaccharides, particularly β-glucans and polysaccharide-protein complexes such as *Coriolus versicolor* polysaccharide peptide demonstrate potent immunomodulatory and anti-tumor effects while their exact mechanism remains unclear. These compounds enhance cell-mediated immunity, act as biological response modifiers and induce immunomodulatory cytokines. Generally, they modulate immunity adaptively: stimulating defenses in cancer/infections while suppressing aberrant responses in autoimmunity. This balanced multi-target action is showing that natural immunomodulators are more promising for treating immune dysregulation diseases in contrasts with synthetic immunosuppressants (Ooi & Liu, 2000).

NATURAL REMEDIES IN AUTOIMMUNE AND INFLAMMATORY DISEASES

Use of Traditional Medicine

Ayurveda, the science of longevity, is an ancient Indian healing system that restores equilibrium between body, mind and spirit. Its holistic approach combines herbal formulations (e.g. turmeric, ashwagandha), purification therapies and lifestyle interventions to address disease pathophysiology. Current research emphasizes that Ayurveda herbs modify several inflammatory pathways by preventing NF-κB, modulating cytokines (TNF- α and IL-6) that further regulate immune responses (Chandran & Goel, 2012; Ahmed et al., 2025). whereas Boswellia serves as an important medicine for inflammatory bowel disease. These pharmacological applications make Ayurveda a most significant supplement in stressed conditions. *Fagopyri Dibotryis Rhizoma* (FDR) is a keystone of Traditional Chinese Medicine that have anti-inflammatory and immunomodulatory properties. In rheumatoid arthritis, FDR extracts reduce the chances of CRP by 38% (Li et al., 2021).

Rheumatoid arthritis (RA) is a prevalent global disorder affecting 0.5-1% of the population and leads to joint destruction. Autoantibodies such as RF and ACPA allow early diagnosis. About 30-40% of patients remain untreated by conventional

therapies. This unmet need drives interest in natural immunomodulators. Compounds like curcumin demonstrate multi-target efficacy in RA, i.e., reducing DAS28 (Disease Activity Score in 28 joints) scores comparably to methotrexate in clinical trials while inhibiting NF-κB, lowering IL-6/TNF- α and modulating ACPA production. Their ability to concurrently address autoimmunity, inflammation and oxidative damage offers advantages over single-pathway biologics, positioning natural products as valuable adjuncts in RA management (Rocha et al., 2019). Furthermore, inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC) arises from an aberrant immune response to gut microbiota in genetically susceptible individuals. While adaptive immunity has long been implicated, innate immune dysfunction such as defects in epithelial barrier in UC and impaired antimicrobial response in CD plays an equally essential role in immune dysfunction. Plague psoriasis is the most common variant arises from dysregulated Th17/IL-23 signaling, driving inflammation and systemic comorbidities like psoriatic arthritis. Mild cases are managed with topical agents (corticosteroids, vitamin D analogues), while biological targeting TNF-α, IL-17 or IL-23 dominates moderate-to-severe disease.

There are some herbal medicinal approaches enhanced by nanotechnology for inflammatory and autoimmune disease. Liposomes and certain nanoparticles improve bioavailability, solubility and targeted delivery of chemicals by reducing toxicity. Flavonoids (e.g. curcumin, resveratrol) reduces the chances of poor absorption by reducing particle size and giving multiple effects against inflammation (Panda & Mohapatra, 2024). Polyherbal compounds ingrained in traditional systems like Ayurveda, when combined with other herbs, enhance its effectiveness and reduces toxicity through synergistic actions. These synergistic mechanisms activate through pharmacokinetic and pharmacodynamic (multi-target). For example, Aloe vera (anti-inflammatory) and Boswellia serrata (inhibition of TNF- α) demonstrate immunomodulatory polyherbalism (Dubey & Dixit, 2023).

Safety and Patient Compliances

According to the guidelines of WHO, the safety of natural medicinal products is primarily assessed by quality control and patient adherence, but still certain challenges persist (e.g. *Ginkgo biloba* with anti-coagulant) and variations in concentrations of bioactive compounds. Some herbs (Aconitum) as compared to normal herbs (turmeric) exhibit toxicity. Enhancing compliance via improved palatable formulations such as microencapsulated curcumin and simplified dosing could reduce their challenges. Standardization of herbal products and public awareness remains in consideration for mitigating these growing risks (Papadakis et al., 2019).

IMMUNOMODULATORY ROLE OF NATURAL PRODUCTS

Flavonoids

Epidemiological studies demonstrated that flavonoid-rich plant foods reduce the risk of chronic diseases. Flavonoids are key mediators of several protective effects. These abundant plant metabolites elaborate potent anti-inflammatory effects by suppressing pro-inflammatory mediators and reducing acute-phase proteins (C-reactive protein). At molecular level, they modulate immune response by inhibiting pro-inflammatory NF-κB and AP-1 pathways as well as activating Nrf2-mediated antioxidant defenses. Beyond direct antioxidant effects, flavonoids concurrently suppress pro-inflammatory cytokines (TNF- α, IL-6) by blocking upstream NF-κB and MAPK signaling. For instance, quercetin's catechol structure enables both ROS scavenging and IKKβ inhibition (Slika et al., 2022). Fig. 1 presents the immunomodulatory effects of flavonoids.

Quercetin is considered a potent flavanol, abundant in onion, kale, broccoli, tea and red wine (Formica & Regelson, 1995). Its anticancer effects demonstrated dual modulation of oxidative stress. In Dalton's lymphoma models, quercetin reduced tumors via apoptosis induction through PKC inhibition (Maurya & Vinayak, 2015). Quercetin modulates immunity by blocking NF-κB and NLRP3 inflammasomes by reducing IL-6 and TNF-α production and stabilization of mast cells. Luteolin is an effective flavone, found in parsley,

celery, bell peppers and carrots (Imran et al., 2019). Its anticancer activity involves dual oxidative stress modulation by showing antioxidative effects i.e. reduces ROS in T24 bladder cancer cells, inactivating mTOR to induce apoptosis, inhibits metastatic Src/Stat3 signaling via ROS scavenging (Fan et al., 2019) and it exerts pro-oxidant selectivity by inhibiting Nrf2 and increasing ROS in cancer cells. Apigenin is abundantly found in parsley, chamomile and celery infusions (Salmani et al., 2017). Apigenin exhibits anticancer and antioxidative properties as demonstrated in Kaposi sarcoma-associated Bcell lymphoma where it alleviates oxidative stress, induces p53 and triggers autophagy (Granato et al., 2017).

Nutritional discrepancies result in metabolic deformities, disrupt the normal immune functions and impairs inflammation-related disorders. Polyphenolic compounds such as phloretin and glabridin alleviate these responses by modulating key inflammatory pathways. Glabridin prevents the generation of NO, TNF-α and IL-1β by blocking the NF-kB/MAPK-mediated dendritic cell growth (Chang et al., 2012). Similarly, phloretin downregulates the activity of IL-8, CXCL10, and TNFα mRNA by activating Nrf2 to upregulate the expressions of antioxidant enzymes (GPx, SOD, HO1) (Chuang & McIntosh, 2011).

Alkaloid

Macrophages, an important component of beneficial immune cells, regulating host defense, tissue balance and certain inflammatory responses. Macrophages that are naturally activated migrate to sites of inflammation, generating ROS and expressing specific antigens to combat invasive pathogens and tumor cells (Kapellos et al., 2019). Sinomenine (SIN) is considered an active alkaloid extracted from *Caulis Sinomenii*. Since decades, it is used as an immunomodulatory agent in China. It acts by suppressing NF-κB via modulation of miR-155/SOCS1 (Yin et al., 2020), upregulation of IκB (Wang et al., 2005), and phosphorylation of p65 inhibition (Lan et al., 2016). Tetrandrine (TET) is generally a bis-benzylisoquinoline alkaloid obtained from Stephania and tetrandra, that expresses its dual properties i.e. anticancer and immunoregulatory properties (Liu et al., 2016). While inducing tumor cell cycle (G0/G1 via p21/cyclin D1 modulation), its primary immune effects include, polarization of macrophages to M1 phenotype through STAT1 activation, disruption of PD-1/PD-L1 axis and potentiation of CD8+ T-cell as well as suppression of Th17 via ROR γt inhibition and expansion of Treg via TGF-β/Smad3.

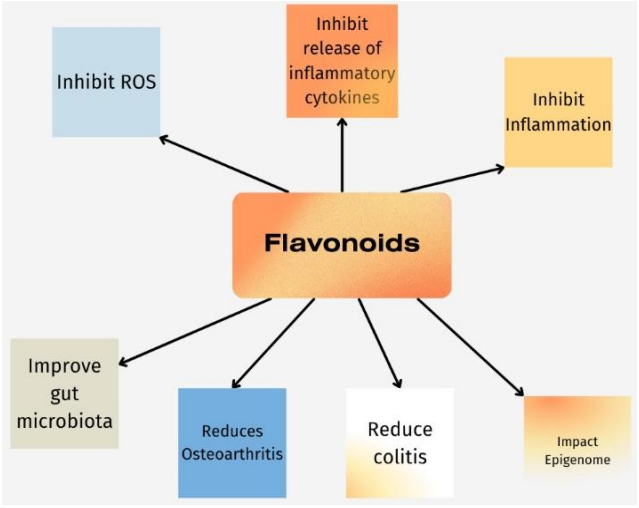

Fig. 1. Schematic representation of the immune-modulatory effects of flavonoids via anti-inflammatory, antioxidant and epigenetic mechanisms

Berberine, a protoberberine-type alkaloid derived from various Berberis species, demonstrates multiple pharmacological properties. It suppresses NF-κB and NLRP3 inflammasome activation by rebalancing Th17/Treg responses particularly associated with chronic inflammation. Its metabolic benefits (e.g., AMPK-mediated insulin sensitization) synergies with immune effects by attenuating adipose tissue inflammation (reducing M1 macrophage infiltration), preserving gut barrier function (preventing endotoxemia) and modulating hepatic Kupffer cell activation.

Terpenes and Terpenoids

Terpenoids or isoprenoids are oxygenated derivatives of terpenes, hydrogen compounds synthesized from dimethylallyl diphosphate and isopentenyl diphosphate (IPP). These structurally diverse metabolites are classified by carbon units, ranging from hemiterpenoids (C5) to polyterpenoids (C >40) and play important roles in immune regulations.

Artemisinin, also known as sesquiterpene lactone characterized by unique peroxide structure, was first derived from *Artemisia annua L.* in 1972

(Shi et al., 2015). Artemisinin and its by-products demonstrate different medicinal properties especially it is used against the malarial disease, making them promising compound for treatment of allergic diseases (Li, 2012). T cells are considered an important mediator for adaptive immune system through signaling of TCR activation, proliferation of IL-2 and ultimate apoptosis, following elimination of pathogen. In autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, survival of T cell could be sustained by persisting autoantigens (Hedegaard et al., 2008). Artemether, an important artemisinin derivative suppresses T cell proliferation and cytokine production (IL-2, IFN- γ) by inhibiting MAPK signaling (ERK1/2, Jnk, P38 phosphorylation) (Wang et al., 2007).

Curcumin

Curcumin is primarily used as a bioactive compound along with demethoxycurcumin and bisdemethoxycurcumin in turmeric. Several studies highlight the importance of curcumin in different serious conditions such as arthritis, cancer and Alzheimer's diabetes (Amalraj et al., 2017). However, it's hydrophobic in nature, fast metabolism and less bioavailability makes it unfavorable for treatment of such applications (Nelson et al., 2017). To address these limitations, applying advanced formulative techniques such as addition of liposomes and certain nanoparticles to boost its absorption and stability (Gopi et al., 2017).

Andrographolide

Andrographolide is a labdane diterpenoid extracted from the plant Andrographis paniculata that has shown potential for various therapeutic uses, including anti-inflammatory, antioxidant, and anticancer properties. Table 1 shows andrographolide and their potential against inflammatory diseases.

Boswellic Acid

Boswellic acid is well-known pentacyclic triterpenes from *Boswellia species*, comprises four primary bioactive forms with AKBA (3-O-acetyl-11-keto-β-BA) exhibiting the strongest activity of immunomodulation. It exerts anti-inflammatory response through 5-lipoxygenase inhibition, NF-κB suppression and downregulation of COX-2/MMP-9. Clinically, they improve the symptoms of

Table 1. Andrographolide and derivatives in inflammatory disease models and mechanisms

Inflammatory Disease Target	Experimental Systems	Proposed Mechanism of Action	Reference
Asthma	Animal models sensitized with ovalbumin	Influences JAK1/STAT3 signaling; lowers IL-6 & IL-17A/F; neutralizes ROS; reduces NF-κB activity & NLRP3 inflammasome activation	Yu et al., 2021
Chronic Obstructive Pulmonary Disease (COPD)	Human immune cells (PBMCs, U937); macrophage models; patient samples	Interferes with PI3K/Akt/NF-κB cascade; enhances glucocorticoid response; boosts Nrf2 pathway; involves SIRT1/ERK modulation	Liu, 2020
Acute Lung Injury	Murine model challenged with LPS	Attenuates inflammation mediated by MAPK and NF-κB pathways	Peng et al., 2016
Acute Lung Injury	Mouse models exposed to cigarette smoke (with/without C5L2 deficiency)	Mitigates DNA damage; stimulates Nrf2/glutathione antioxidant system	Liu et al., 2018
Pulmonary Fibrosis	Murine bleomycin model; human lung fibroblasts (MRC-5)	Counters epithelial-mesenchymal transition (EMT); decreases fibroblast activation	Karlate et al., 2018

rheumatoid arthritis (260 patients), Crohn's disease indices and asthma biomarkers by modulating the balance of Th1/Th2 (Moudgil & Venkatesha, 2022). While promising, <5% oral bioavailability necessitates advanced delivery systems like BA-phospholipid complexes (2.8 × absorption) and nanoparticles (3.5 ×AUC increase). Additionally, they show anti-tumor potential via p53-independent apoptosis and NF-κB-regulated gene modulation (Rajabian et al., 2023).

PATHWAY MODULATION

Terpenes and their derivatives modulate immune responses via NF-κB, MAPK and JNK pathway. Notable immunomodulatory terpenes include artemisinin, andrographolide and boswellic acids. Natural products often exhibit synergistic interactions through multi-target modulation, bioavailability enhancement and dose-reduction mechanisms (Bonincontro et al., 2023). AP-1 is a dimeric transcriptional factor activated through MAPK signaling, regulated by different cytokines and is effectively suppressed by curcumin, resveratrol and EGCG. Natural compounds scavenge AP-1-activating ROS, prevent subunit phosphorylation, enhance MAPK phosphatase expression (Gazon et al., 2018).

Toll-like receptors (TLRs) serve as crucial sentinels of innate immunity, distinguishing pathogenic patterns. Upon activation, TLR signaling triggers both NF-κB and MAPK pathways, leading to cytokine production (Manik & Singh, 2022). Natural products modulate these through TLR4 antagonism, MAPK inhibition and TRAF6 inhibition (Xiao et al., 2024). Curcumin, andrographolide and berberine demonstrate significant anti-inflammatory effects in sepsis and arthritis. T-regulatory (Treg) cells maintain immunological tolerance. Natural products like curcumin, resveratrol and sulforaphane increases FOXP3 expression by increasing Treg population (Chávez & Tse, 2021). Dendritic cells (DCs) work as potent antigen-presenting cells and are used to determine immune responses by differentiating into either inflammatory or tolerogenic phenotypes. Their maturation enhanced the antigen processing via MHC I/II, upregulated the co-stimulatory molecules (CD40, CD80/86) and polarized cytokine secretion (IL6, IL-12, TNF- α) (Coutant & Miossec, 2016). This plasticity makes DCs key targets for natural immunomodulators:

Curcumin promotes tolerogenic DCs by inhibiting NF-κB and AMPK pathways, reducing

CD80/86 expression and enhancing the production of IL-10. Resveratrol suppresses inflammatory DCs via SIRT1-mediated metabolic reprogramming, decreased IL-12 secretion and downregulated the migration of CCR7. Astragalus polysaccharides modulate DC maturation by TLR4-dependent cytokine regulation, balanced the expression of MHC II and enhanced the antigen crosspresentation (Ginhoux et al., 2022). Clinical evidences shows that EGCG from green tea reduces DC activation in rheumatoid arthritis and Berberine inhibits DC-mediated Th17 differentiation in psoriasis along with Boswellic acids that prevent DC migration in multiple sclerosis model. These natural compounds maintain DC surveillance without overactivation, preserve self-tolerance, modulate co-stimulatory molecule balance and regulate DC-T cell interaction dynamics (Liu et al., 2022).

Natural antioxidants including vitamin E, polyphenols and carotenoids enhance immune function through multiple protective mechanisms. These compounds neutralize ROS that damage immune cells, modulate redox-sensitive pathways, preserve membrane integrity by prevention of lipid peroxidation and regulate immune cell signaling (Khadim & Al-Fartusie 2021). Vitamin E demonstrate particular efficacy by enhancing humoral and cellular immunity, improving vaccine responses (enterotoxemia protection in sheep) and maintaining phagocytic function under oxidative stress.

Other potent immunomodulatory antioxidants include curcumin that upregulates GSH and SOD, resveratrol that activates SIRT1-mediated cytoprotection and quercetin that stabilize mast cells and reduces histamine release (Li et al., 2020). Recent studies shows that vitamin E supplements improve elderly immune responses, curcumin enhances post-vaccination antibody titers and green tea polyphenols reduce inflammation in autoimmune conditions. These effects are mediated through protection of immune cell membrane, modulation of cytokine production, maintenance of

optimal redox balance and enhancement of antigen presentation (Tengerdy, 1989).

CLINICAL EVIDENCE AND TRANSLATIONAL POTENTIAL

Clinical trials are conducted to evaluate new treatments in living organism especially humans and progress through multiple phases to assess safety and efficacy measures. Phase 1 trials involve small patient cohorts (20-80 patients) across varying dose levels to determine treatment safety and tolerability (Rubinstein, 2014). Phase 2 trials expand to a few hundred patients, assessing preliminary efficacy and further safety to determine whether the treatment warrants advancement to large-scale. Key considerations in phase 2 trial design include therapeutic mechanisms (e.g. cytotoxic, immunomodulatory or biomarker-dependent therapies), trial objectives (e.g. treatment selection or progression to phase 3) and outcome measures (e.g. binary or time-to-event endpoints). Trial structure is affected by some practical considerations such as primary inhibitory rules, protocols of randomization and availability of prior data (Yan et al., 2018). A comparative study of two different phase designs demonstrates the important decision points. Subsequently, phase 3 trials are conducted to approve therapeutic effectiveness in larger populations, whereas phase 4 studies assess long-term effects following regulatory approval. Natural products having anti-inflammatory properties such as curcumin or omega-3 fatty acids have been considered across these trial phases, representing their translational potential in clinical applications (Torres-Saavedra & Winter, 2022).

Ferroptosis is considered an iron-dependent form of regulated cell death driven by lipid peroxidation, offers a novel therapeutic strategy for cancer resistant to apoptosis (Chen et al., 2023). While synthetic compounds and nanomedicine formulation (e.g. inorganic nanoparticles) can induce ferroptosis, natural products such as artemisinin, curcumin and withaferin A also modulate this pathway through anti-inflammatory and immunomodulatory mechanisms. These agents disrupt iron homeostasis which can amplify oxidative stress and synergize with conventional therapies, e.g. chemotherapies (chemotherapy, immunotherapy), to enhance tumor cell death (Piccolo et al., 2024). Importantly, ferroptosis is closely interconnected with the tumor immune microenvironment where natural compounds like epigallocatechin gallate release damageassociated molecular patterns which in turn stimulate antitumor immunity (Zheng et al., 2023). Their synergistic effects with nanomedicine such as polyphenol-based nanoparticles give a promising approach to overcome challenges related to bioavailability while exploiting both ferroptotic and immunogenic effects. Future studies should emphasize clinical trials assessing polyphenols-based ferroptosis inducers predominantly in combination with established medicated modalities to transform laboratory findings and therapeutic applications.

CHALLENGES AND FUTURE DIRECTIONS

Dendrobium officinale show distinct regional chemotypic differences that confounds its standardization: GC-MS profiling across four Chinese provinces recognized 101 volatiles with hexacosane extending approximately 23-34% (lower in Jiangxi and high in Yunnan) (Liu et al., 2020). Medicinal components are evidenced by these regional chemotypic differences. Samples of Yunnan contained three therapeutic compounds whereas there is no detectable compound that appeared in Jiangxi. These geographical differences in their chemical structure affect the development of natural products. While, modern technologies such as specie verification by DNA barcoding, quality control by metabolomic analysis could be used to evaluate these variations by applying herbal medications (Mohapatra et al., 2024). For example, different formulation approaches result in the development of systemic availability of curcumin following oral administration.

CONCLUSION

The assessment of natural products having anti-inflammatory and immunomodulatory properties has exhibited a diversity of bioactive constituents accomplished by modifying key inflammatory pathways i.e. NF-κB, COX-2 and cytokine signaling. Preclinical and clinical investigations indicate the therapeutic value of phytochemicals i.e. resveratrol, curcumin, flavonoids and terpenoids in

the treatment of chronic diseases, autoimmune pathologies and immune dysregulations. However, challenges including limited bioavailability, molecular instability and inter-batch differences in plant-derived products restrict their curative reproducibility. Emerging formulations approaches such as synergistic effects, nanoencapsulation and phospholipid complexes demonstrate the promising strategies to promote pharmacokinetics profiles of these natural compounds. In spite of advantageous evidence, its possible efficacy and safety should be well addressed by rigorous standardization, well-designed clinical trials and regulatory harmonization of natural compounds. The incorporation of omics technologies and target-directed purification can further improve the identification of active constituents while studying natural product-drug interactions.

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