Review

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Review

Biomacromolecules as Immunomodulators: Utilizing Nature's Tools for Immune Regulation

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Abstract: Although there are numerous available immunomodulators, those of natural origin would be preferable based on their safety profile and effectiveness. The research and clinical interest in immunomodulators have increased in the last decades, especially in the immunomodulatory properties of plant-based therapies. Innovative technologies and extensive study on immunomodulatory natural products, botanicals, extracts, and active moieties with immunomodulatory potential could provide us with valuable entities to develop as novel immunomodulatory medicines to enhance current chemotherapies. This review focuses on plant-based immunomodulatory drugs that are currently in clinical studies. However, further studies in this area are of utmost importance to obtain complete information about the positive effects of medicinal plants and their chemical components and molecules as an alternative to combatting various diseases and/or prevention.

Keywords: plant immunomodulator; medicinal plant; immunomodulation; resveratrol; curcumin; quercetin; capsaicin; andrographolide; colchicine

1. Introduction

Plants and their essential chemical ingredients have been used since ancient times because of their enormous therapeutic potential. Natural products have also been utilized for immunomodulatory activities. Polysaccharides, flavonoids, alkaloids, glycosides and other phytochemicals are reported to be mainly responsible for the immunomodulatory activity of plants [1]. They can act as lead molecules for developing safe and effective immunomodulators for disease prevention and treatment.

Immunity is the natural defense system against various infections and agents that efficiency is influenced by exogenous and endogenous factors associated with immunostimulation or/and immunosuppression. The agents that can help to normalize or modulate immune mechanisms and pathophysiological immune processes are called immunomodulators [1]. They are chemical synthetic and biological biomolecules capable of modulating, suppressing or/and stimulating innate or adaptive immunity components, therefore known as immunomodulators, immunoaugmentors, immunorestoratives, or other modifiers of biological response [2,3]. All of them have specific activities and can be useful in increasing the effectiveness of a vaccine, preventing allergies and infections or controlling the pathological immune response after organ transplantation. Monoclonal antibodies and chemically synthesized compounds/drugs are also used as immunomodulators. However, there are side effects and major limitations to their general use [4–6]. Because of these effects, natural immunomodulators can potentially replace them in treatments.

The prevention or/and treatment of different diseases using plant-based drugs have been reported throughout human history. In all cultures and throughout all ages, parts of different plants or whole plants have been used as medicines to treat a wide range of ailments [7–10].

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Not enough studies show the distribution of specific medicinal plants in specific geographical areas and how they are implemented and used in medicine. Therefore, systematic reviewing of published studies can help identify the central geographical regions of medicinal plants used to alleviate various diseases. Moreover, further studies on them and their compounds are needed.

This review focuses on current literature on selected medicinal plants and single plant chemicals with immunomodulatory activity, studied in clinical trials, and their therapeutic potential and effects in various diseases. The search was conducted from the most commonly used scientific databases, and the crucial aspects of the scientific topic were summarized.

2. Immunity, Immune System and Immunomodulators

The immune system maintains the organism`s homeostasis together with other systems, where numerous exogenous and endogenous factors affect immune function and mechanisms and can either inhibit or stimulate them. In line with this, immunomodulators can normalize or modify immunological processes [11].

Plant immunomodulating properties have received increased research attention in recent years owing to a growing awareness of the importance of immune system modulation in immune-mediated diseases therapy and prevention. Several well-known plant remedies in traditional medicine have not only direct effects on the pathogens but also can stimulate the host's innate and adaptive defense mechanisms [12].

Immunomodulators can come from different sources and serve to alter various immune mechanisms [13]. In clinical practice, immunomodulators are classified as immunoadjuvants, immunostimulants, and immunosuppressants. As immunoadjuvants are particular immune stimulators that improve vaccine effectiveness, immunostimulants are agents that activate or induce immune system mediators or components. Immunostimulants can boost resistance to cancer, allergies, infections, etc. Immunosuppressants, which are chemicals that inhibit the immune system, on the other hand, can be utilized to control the abnormal immunological reaction that occurs after organ transplantation, autoimmune disorders, infection-related immunopathology, hypersensitivity reactions, etc. [11]. As a result, immunomodulatory agents with antioxidant and anti-inflammatory activity have received much attention as potential chemopreventive agents because of their ability to counteract chronic inflammation, creating favorable conditions for the transition from normal to the cancer cell [14]. However, most synthetic immunomodulators have substantial toxicity or other adverse effects; thus, plant-derived immunomodulators are being discussed as safer substitutes [15].

A recent evidence-based review demonstrated the multiple and pleiotropic effects of essential plant-derived nutraceuticals on the immune system [13]. Di Sotto et al. focused on the adjuvant use of plant-derived immunomodulators, such as polysaccharides, fatty acids and labdane diterpenes, which are usually more tolerable than pharmacological treatments. Furthermore, they provided basic and clinical evidence to support their use in the practice [13]. We present the most common plant immunomodulators and their effects on the immune system in Figure 1.

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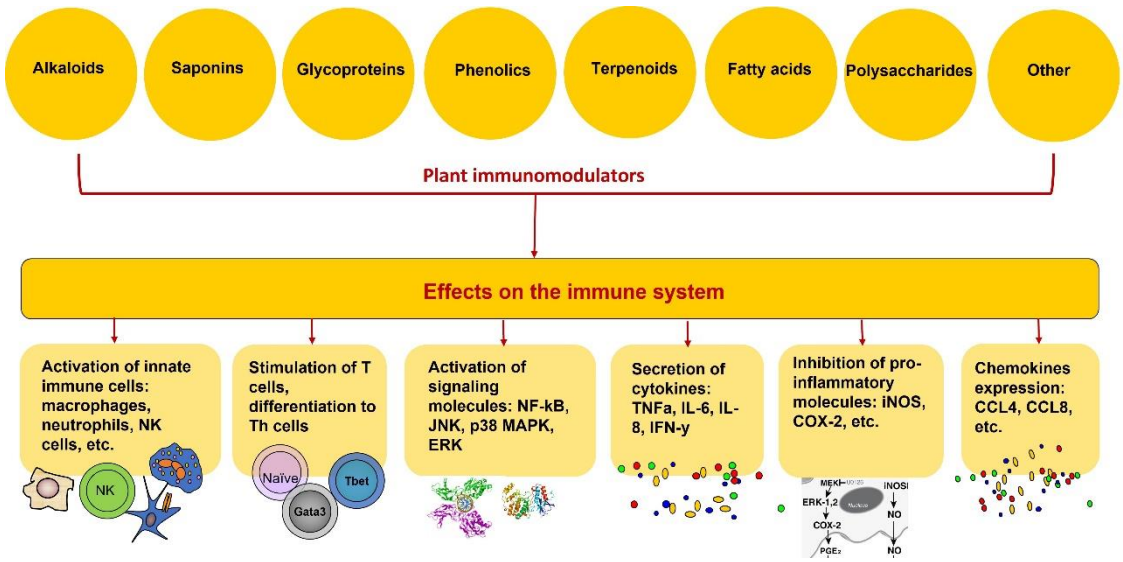

Figure 1. Effects of plant-derived immunomodulators on different immune mechanisms.

Currently, the research is focused on plant biochemicals, biologics, or single molecules as lead compounds that target specific targets associated with a disease.

In contrast, single-molecule compounds with high selectivity, efficacy, and low toxicity for particular molecular/cellular targets and illnesses are difficult to obtain. As a result, the discovery and development of therapeutic candidates from various conventional, complementary, and alternative plant sources are on the rise [16].

3. Selected Medicinal Plants with Immunomodulatory Activity

Plants have been used to prevent and treat external and internal diseases for centuries. They are rich in phytochemicals such as polysaccharides, flavonoids, terpenoids, alkaloids, glycosides, saponins and lactones [11] which form the basis for scientific research of their immunomodulatory properties for the treatment of numerous diseases [17,18].The phytochemical immunomodulatory potency is mainly through modulation of the functions of the macrophages, B and T lymphocytes, dendritic cells, etc. For example, the carbohydrate-binding protein Concanavalin A lectin from *Canavalia ensiformis* (f. Fabaceae) can activate T lymphocytes by cross-linking the TCR/CD3 glycoproteins. At the same time, the catechins, epigallocatechin-3-gallate, and epigallocatechin, from *Camellia sinensis* suppressed cytokine secretion and T-lymphocyte proliferation by activator protein 1 (AP-1) inactivation through the extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinase (JNK) pathways [19,20].

Some of the medicinal plants that attracted the attention of scientists are *Withania somnifera* (ashwagandha), *Tinospora cordifolia* (guduchi), *Piper longum* (pippali), *Ocimum sanctum* (tulsi), *Camellia sinensis* (green tea), *Andrographis paniculata*, *Carthamus tinctorius (safflower)*, *Sophora alopecuoides* (Kudouzi), *Sinomenium acutum*, *Astragalus membranaceus*, *Panax ginseng*, *Lycium barbarum*, etc. [11,17,18]. They are used mainly in the Indian traditional system, known as Rasayana and the traditional Chinese systems. Their analyses demonstrate different immunomodulatory activity and antioxidant, anti-inflammatory, antiasthmatic, antiarrhythmic, hepatoprotective, antifungal, and many other medicinal activities. For example, *Withania somnifera* (f. Solanaceae) is widely used alone or in combination with other herbs in the Indian Ayurvedic and the Chinese medicinal system to treat numerous conditions in humans. Pharmacological analyses have shown it is a reservoir of steroidal lactones known as withanolides which are found to stimulate immunological activity and phagocytic activity by mobilizing and activating macrophages and inducing the proliferation of spleen cells in mice [21,22]. Also, they, along with other *W. somnifera* phytochemicals like anaferine and β-sitosterol, have neuroprotective protentional which can be useful in treating Alzheimer's disease by blocking the production of amyloid beta (Aβ) by inhibiting the nuclear factor-kB, restoring

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synaptic function, and improving antioxidant effects through the migration of erythroid 2-related factor 2 (Nrf2) [23]. Another folk medicine plant, *Tinospora cordifolia* (f. Menispermaceae), which is a deciduous climbing shrub indigenous to India, is used to combat acute and chronic inflammation. Plant extracts have been isolated from over 200 phytochemicals with immunomodulatory protection on key signaling pathways related to cell proliferation and inflammation [21,24,25]. For example, its polysaccharide G1-4A induces in vitro surface expression of MHC-II and CD-86 in mice macrophages. Thus they significantly increased the levels of proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), interleukin 12 (IL-12), interferon-gamma (IFN-γ) and nitric oxide (NO) and decreased levels of Th2 cytokines like interleukin 4 (IL-4) [26]. The other family member – *Tinospora crispa*, has been shown to contain more than 65 different compounds, including flavonoids, lactones, furanoditerpenes, alkaloids, lignans, and steroids, such as magnoflorin, syringin, cardioside, quercetin, eicosenoic acid, boldine, that have antioxidant potential higher than ascorbic acid, and are responsible for activating the immune system by increasing the expression of IL-6, interleukin 8 (IL-8), and INF-γ [20]. The pharmacological studies of the whole plant, root, and seed extracts of *Sophora alopecuroides* (f. Fabaceae), a subshrub-like desert plant widely distributed across west and middle Asia, have shown a wide variety of activities as anti-inflammatory, antibacterial, antiviral, antioxidant, cardioprotective, and neuroprotective [27]. Also, they show the antitumor effect by modulating the cancer signaling and molecular pathways or targeting various cancerous cells and inhibiting the cell growth, arresting the cell cycle, enhancing the apoptosis and cellular differentiation, and inhibiting cancer metastasis and invasion [28]. It was shown that the main chemicals and active components of *S. alopecuroides*, the alkaloids aloperine, matrine, oxymatrine, sophoridine, and sophocarpin, at high doses, exert an immunosuppressive effect and at low doses – immunostimulation [28,29]. One of the most representative Chinese herbs with great therapeutic potential is the liana *Tripterygium wilfordii* (f. Celastraceae). Although it is poisonous and shows acute toxicity when consumed, the plant's root extract has excellent anti-inflammatory and immunosuppressive properties. It is widely used for treating various inflammatory and autoimmune disorders [30]. More than 100 compounds have been isolated from its root extract, mainly alkaloids, and terpenoids, that show great effectiveness in treating rheumatoid arthritis [28]. As lipids play an important role in the pathogenesis of rheumatoid arthritis, some research suggested the *T. wilfordii* extract modulates the formation of lipid mediators in the innate immune cells [31]. *Panax ginseng* (f. Araliaceae) is a perennial herb native to Korea and China and one of the most extensively studied. Its clinical analyses demonstrate that it improves immune function and has anti-inflammatory, antioxidant, and anticancer effects. Although all parts of the plant contain pharmacologically active compounds, the roots are the richest in them. The main compound – polysaccharide ginseng, enhances the production of cytokines, including TNF-α, IL-1β, IL-6, and IFN-γ and reactive oxygen/nitrogen components such as NO and hydrogen peroxide (H2O2) and thus stimulates the phagocytic activity of macrophages [32,33].

The modern pharmacological analyses on the immunomodulating activity of the herbs from plant-based African and American-Indian medicines are focused on *Catharanthus roseus*, *Acacia senegal*, *AMahonia aquifolium*, *Centella asiatica*, *Aspalathus linearis* (Rooibos), *Harpagophytum procumbens*, *Kalanchoe pinnatas*, *Pelargonium sidoides*, *Capsicum species*, *Taxus brevifolia*, *Psidium guajava*, *Uncaria tomentosa* (cat's claw), *Cordia* species and many more. *Catharanthus roseus* (f. Apocynaceae), a native and endemic to Madagascar, but grown worldwide as an ornamental plant, is well-known for its variety of beneficial activities as an antioxidant, antibacterial and antifungal. Its most attractive compounds – the bisindole alkaloids vinblastine, vincristine, and vindesine, show antidiabetic and anticancer activity [17,34]. These alkaloids are highly toxic and block the metaphase of mitosis by binding to tubulin and preventing the microtubule assembly of the spindle [35]. *Centella asiatica* (f. Apiaceae) is a tropical plant used for wound healing in many cultures, including Ayurvedic, Chinese, Japanese (Kampo), and African. Its healing effect is due to the anti-inflammatory potential of its main phytochemicals asiaticoside, and madecassoside [35]. As scientific research demonstrates, these triterpene glycosides inhibit the proinflammatory mediators and cytokines, as well as reactive oxygen species (ROS), NO, TNF-α, and IL-1β in macrophages and keratinocytes in vitro [36]. Another tropical

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herb *Uncaria tomentosa* (f. Rubiaceae), from the highlands of the Peruvian Amazon has been reported to be effective as an immune system rejuvenator, antioxidant, antimicrobial, and anti-inflammatory. It is rich in many phytoconstituents with immunomodulatory properties such as glycosides, organic acids, sterols, triterpenes, and spiroindole alkaloids (isopteropodine and rynchophylline) and has been used to treat knee and rheumatoid arthritis in humans [11,37]. One of the most recognized medicinal plants worldwide is *Echinacea purpurea* (f. Asteraceaeis), a flowering plant native to North America. Its products are commercially sold worldwide as a general health promoter and for its preventive actions against cold and flu [38]. The scientific analyses of the plant demonstrate significant immunostimulatory and anti-inflammatory, antioxidant, hypoglycemic, and antiproliferative activities. Its phytochemical constituents as glycoproteins, polysaccharides, phenolic compounds, caffeic acid derivatives, and alkylamides stimulate the antiviral activity and the body's immune system by influencing macrophages, dendritic cells, monocytes, and NK cells [20].

Nigella sativa, Glycyrrhiza glabra, Hypericum perforatum, Achillea millefolium, Mentha piperita (peppermint), Colchicum autumnale, Galanthus nivalis, Chamomilla recutita, Primula officinalis, Cotinus coggygria, Plantago major, etc. are among the European herbs with immunomodulatory and anti-infection potential [39]. One of the most popular and widely used is Mentha piperita (f. Lamiaceae), a native to Europe but cultivated and naturalized in all European countries and North America. Its pharmacological research demonstrated a wide range of properties, including antioxidant, antitumor, antiallergenic, antimicrobial activities, antiparasitic, and immunomodulatory [40,41]. In vitro assay with an M. piperita ethanol extract has shown a decreased production of TNF-α, IL-6, NO, and prostaglandin E-2 (PGE-2) in a mice macrophage cell culture [39]. Another plant, native to Europe and Southwest Asia, is Galanthus nivalis (f. Amaryllidaceae), whose abundance of bioactive compounds such as flavonoids, phenols, terpenoids, and alkaloids is attractive for scientific research because of their wide range of pharmacological potential. One of the main active compounds, the alkaloid galantamine, has antimicrobial, antioxidant, and anticancer activity and is used (as the drug Nivalin) for the symptomatic treatment of Alzheimer's disease and other memory impairments [42]. The smoke tree or Cotinus coggygria (f. Anacardiaceae), a shrub growing wildly in Southeast Europe and the Caucasus to central China, is rich in various bioactive secondary metabolites such as flavonoids, aurones, chalcones, anthocyanins, and catechins, and is an important source of essential oils and extract with different health-promoting properties [43]. In vitro and in vivo analyses on the phytochemistry and bioactivity of the extracts from different plant parts revealed their wound-healing, anti-inflammatory, immunostimulatory, antimicrobial, cytotoxic, antioxidative, hepatoprotective, and antidiabetic effects [44].

Many plants under high throughput screening for an assessment of pharmacologically important molecules are spices used in culinary worldwide. *Allium sativum* (garlic), *Thymus species* (thyme), *Origanum vulgare* (oregano), *Ocimum basilicum* (basil), *Petroselinum crispum* (parsley), *Anethum graveolens* (*dill*), *Salvia rosmarinus* (rosemary), as well as *Piper nigrum* (black pepper), *Cinnamomum zeylanicum* (cinnamon), *Curcuma* species (turmeric), *Zingiber officinale* (ginger) and many more are known to be natural immune boosters. The presence of more than 200 bioactive constituents, including organosulfur, saponins, and polysaccharides, gave *Allium sativum* (f. Amaryllidaceae) significant therapeutic potential like antioxidant, anti-inflammatory, anticancer, and immunostimulant [45]. The high polysaccharide contents give garlic a strong immunomodulation activity by the expression and proliferation of cytokine genes and by enhancing the cytotoxicity of macrophages and lymphocytes [20,45]. *Salvia rosmarinus*, *Salvia officinalis*, *Origanum vulgare*, *Ocimum basilicum*, and *Thymus* species, all from the family Lamiaceae, have good to moderate immunomodulation and antiviral activities as well as antioxidant, anti-inflammatory, antidiabetic, antimicrobial, and anticancer [46,47]. For instance, oleanolic acid in *S. rosmarinus*, safficinolide, α-pinene, and β-myrcene in *S. officinalis*, and carvacrol from *O. vulgare* has been proven to have a good effect against viruses, *O. basilicum* shows antioxidants and anti-inflammatory properties and *P. crispum* (f. Apiaceae) has antioxidants and antibacterial properties [18,47]. *Curcuma* species (f. Zingiberaceae) are a popular dietary spice and are widely used in traditional medicine to treat diverse immune-related disorders. The scientific studies on its main polyphenolic compound, curcumin,

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reveal its antioxidant, antibacterial, and anti-inflammatory activity [11]. Curcumin has shown remarkable efficacy in treating cerebral malaria through immunomodulation mechanisms [48]. It inhibits NF-κB activation and reduces pro-inflammatory cytokine production in endothelial cells [11,18,48]. *Cinnamomum zeylanicum* (f. Lauraceae) is an evergreen tropical bush native to Sri Lanka, West India, Sumatra, and South America, and its immunomodulatory phytoconstituents cinnamaldehyde, eugenol, phellandrene, benzaldehyde, cumin aldehyde, and terpenes, modulate the immunoglobulin levels, and both cell-mediated and humoral immunity [18].

Many more plants not discussed above have immunomodulatory potential. The more popular among them, along with their regional sources, bioactive constituents, and other reported biological activities, are given in Table 1.

Table 1. List of selected plants with immunomodulatory activity.

Botanical name/Family.	**Source countries**	**Part used**	**Bioactive-chemical constituent**	**Biological activity**	**Reference**
Acacia catechu/ Fabaceae	India, East Africa	leaves, bark	flavonoids (quercetin, catechin, epicatechin)	antioxidant, immunomodulatory, hypoglycaemic	[17,35,49]
Achillea millefolium/Compositae	Northern Hemisphere	whole plant	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes, lactones	anti-inflammatory, antispasmodic, antipyretic, diuretic	[50,51]
Andrographis paniculata/Acanthaceae	India, Sri Lanka	whole plant, leaves, stems, roots	diterpenoids (andrographolide), lactones, flavonoids, polysaccharides	immunomodulatory, hepatoprotective, antispasmodic, anticancer, anti-inflammatory, antiviral, anti-proliferative, anti-platelet	[52,53]
Aronia melanocarpa/ Rosaceae	North Amerika	fruits, bark, leaves	flavonoids (procyanidins anthocyanins), catechins, phenolic acids, ascorbic acid	immunomodulatory, anti-inflammation, antioxidant, gastroprotective, hepatoprotective, antiproliferative, cardiovascular-	[20,54,55]

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				protective, antioxidants	
Pelargonium sidoides/ Geraniaceae	South Africa	roots, shoot, leaves	coumarins, phenols	immunomodulatory, antibacterial	[35,56]
Zingiber officinale/ Zingiberaceae (ginger)	Asia	roots, leaves	phenolic acid (eugenol, gingerols, shogaols, paradols) lactons, terpenes	immunostimulation, antimicrobial, antioxidant, analgesic, anti-inflammatory, anticancer, antihypertensive	[57,58]
Kalanchoe pinnata/Crassulaceae	Madagascar	leaves, flowers	flavonoid glycosides (quercitrin), bufadienolides, lectins, polyphenols	immunosuppressive, antifungal, antimicrobial, antiviral, wound healing (antiscar), anti-inflammatory	[59,60]
Camellia sinensis/Theaceae (green tea)	China, India, Nepal	leaves	catechins (epigallocatechin-3-gallate, epigallocatechin, epicatechin), triterpenoids, saponins	immunomodulatory, antioxidant, antiviral, anticancer, antifungal activities.	[20]
Cannabis sativa/Cannabaceae	Central Asia, widely cultivated around the world	leaves, seeds, inflorescence	cannabinoid (cannabidiol, cannabigerol, Δ9-tetrahydrocannabinol), terpenes, flavonoids	anti-inflammatory, immunosuppressive, neuroprotective, antioxidant	[61,62]

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Capsicum species/ Solanaceae	Central and South America	fruits	provitamin A, vitamins (E, C) carotenoids, phenolic compounds (capsaicinoids, luteolin, quercetin)	antioxidant, antimicrobial, antiseptic, anticancer, counterirritant, antioxidant, immunomodulator	[37]
Cyclopia genistoides/Fabaceae (Honeybush)	South Africa	flowers, leaves, stems	phenols, flavones, flavanones isoflavones, xanthones (mangiferin), coumestans, catechins (epigallocatechin-3-gallate), benzaldehyde derivates, phytoestrogens	immunomodulatory, anti-inflammatory, antioxidant, anti-proliferative, anticancer, cytoprotective	[63,64]
Euphorbia hirta/Euphorbiaceae	India, Australia	herb, leaves, roots	flavanoid glycoside, phenolic acids, alkaloids	anticancer, antioxidant, antibacterial, antifungal, antimalarial, anti-inflammatory, antiasthmatic	[17,54]
Ginkgo biloba/ Ginkgoaceae	China	leaves, seeds	flavonoids, terpenoids, alkylphenols, anthocyanidins, lignans, polyprenols polysaccharides, 4′-o-methylpyridoxine	immunomodulatory, antioxidants, anti-inflammation, anticancer, antidiabetic, antilipidemic, antimicrobial, anti-lipid peroxidation, antiplatelet, hepatoprotective, neuroprotective	[66]

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Jatropha curcas/Euphorbiaceae	Mexico, Central America, Brazil	leaves, roots, stems	phenolics, flavonoids, sterols, saponins, phorbol esters, cyclic peptides, lignans, alkaloids, coumarins, terpenes	anti-inflammatory, antimicrobial, antioxidant	[67,68]
Lycium barbarum/Solanaceae (Goji berry)	China, Asia, Europe	fruits, leaves, roots	polysaccharides, scopoletin, carotenoids, flavonoids, vitamins	antioxidant, antiviral, anticancer, anti-inflammatory, cardioprotective	[20,69]
Matricaria chamomilla/ Asteraceae	Southeast Europe	flowers	terpenoids (α-bisabolol, chamazulene), flavonoids sesquiterpenes, coumarins, polyacetylenes	immunomodulatory, antioxidant, anti-inflammatory antiseptic, antispasmodic	[70,71]
Mahonia aquifolium/Berberidacea	Eastern Asia, North and Central America	leaves, bark	alkaloids, phenolics, flavonoids, quinones, vitamins, coumarins	anti-inflammatory, antifungal, antimicrobial, antiproliferative, hepatoprotective, analgesic antioxidant	[72,73]
Morus alba/Moraceae	Central and Eastern Asia, Caucasus, widely cultivated around the world	fruits, leaves, bark	flavonoids, anthocyanins, saponins, alkaloids, tannins, phenolic acids, anthocyanins, ascorbic acid, β-carotene	anticancer, antimicrobial, antidiabetic, immunomodulatory, cardioprotective, hepatoprotective, hypocholesterolaemic,	[17,74,75]

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Vaccinium vitis-idaea/Ericaceae	Baltic countries (Europe), Russia, Canada	leaves, fruits	phenolic, arbutin, flavonol glycosides, proanthocyanidins	antioxidant	[76]
Cetraria islandica/ Parmeliaceae	Europe, North America	seeds, fruits, roots, leaves, stems,	dibenzofuranos, depsidones, fatty acids (lichesterinic acid, protolichesterinic acids), depsides, terpenes	immunomodulatory, antioxidant, cytotoxic, genotoxic, antigenotoxic antimicrobial, anticancer, antidiabetic, anti-inflammatory	[77]
Lavandula angustifolia/ Lamiaceae	Europe	stems, flowers	terpenes, polyphenols (rosmarinic acid, caffeic acid, lavandufurandiol, lavandunat), coumarins, flavonoids (apigenin, luteolin glycosides, catechin)	immunomodulatory, antioxidant, anti-inflammatory, analgesic, antibacterial	[78]

4. Selected Plant Chemicals with Immunomodulatory Activity in Clinical Trials

Most research still focuses on biochemicals or individual plant compounds for specific diseases. It is challenging to use only one plant compound with high selectivity, efficacy and safety for many illnesses. A part of them have been tested in vitro and in vivo [11], but more studies are needed before they can be approved and used as primary and adjunctive therapy for many diseases. In this section, we focused on some selected plant-derived anti-inflammatory compounds that have also been tested in clinical trials.

4.1. Resveratrol

Resveratrol is known as (5-[(E)-2-(4-hydroxyphenyl) ethenyl] benzene-1,3-diol). It was first isolated and identified in 1940 from the roots of Veratrum grandiflorum O. Loes [79]. It is found in various foods and plants such as grapes, red wine, peanuts, blueberries, bilberries, cranberries, pomegranates, soybeans, dark chocolate etc. [80]. It has anti-inflammatory, antimicrobial, antiangiogenic, antidiabetic, chemopreventive, anti-cancer, anti-neurological and antioxidant properties [81–88]. Resveratrol has been shown to reduce lipid synthesis in the liver [89]. It inhibits the platelet aggregation thereby potently blocking reactive oxygen species (ROS) by human polymorphonuclear leukocytes [90]. Resveratrol immunomodulatory activity is associated with the inhibition of NF-κB cells, epithelial (HeLa) cells, TNF-α-mediated macrophage, myeloid (U-937),

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Jurkat, and dendritic cells [91–95]. Resveratrol decreases COX-2 expression and iNOS levels in cytokine-stimulated human airway epithelial cells [95], as well as COX-2 expression in melanocytes by attenuating the ERK1/2 and PI3K/AKT pathways [96] In addition, the IL-1, IL-6, IL-12 and TNF-α production in lymphocytes and macrophages was also inhibited by resveratrol [97,98]. Inhibition also occurs in the expression of adhesion molecules, such as ICAM-1 [99].

The resveratrol mechanisms are described by Zhang et al. [100]. They show the pathways of its action and which functions/processes it has irreplaceable effects. Resveratrol's use as a therapeutic agent has been widely researched in preclinical studies (in vitro models and animal models) [101–106]. Research conducted on in vivo animal models has also increased over the years. The most important of them are associated with preventing and delaying cancer, neurodegenerative diseases, cardiovascular diseases and aging [107–114]. A search for "resveratrol and cancer" in PubMed returns over 4,439 results as of December 2022. However, if we limit the search only to clinical trials, only 28 results have been shown. In 2019, Singh et al. discuss the clinical trials from the published articles [115].

In addition, the available clinical trials with resveratrol are about 192 on https://www.clinicaltrials.gov/ct2/results?cond=&term=resveratrol&cntry=&state=&city=&dist= . They show the benefits of resveratrol in different types of cancer, cardiovascular and neurological diseases, diabetes, metabolic syndrome, hypertension, kidney diseases, nonalcoholic fatty liver syndrome, polycystic ovary syndrome, obesity and inflammation, etc.

4.2. Curcumin

Curcumin (1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E)), a natural polyphenol extracted from the rhizomes of Curcuma longa, has long been in the center of researchers' attention due to its therapeutic and pharmacological properties. For the first time, the molecule exhibited antibacterial activity in 1949 [116]. Furthermore, it has been proven to have anti-inflammatory, antiviral antimicrobial, antiatherosclerotic, antiarthritic, antioxidant, antidepressant and wound-healing effects [117–121].

Curcumin interacts with Toll-like receptors (TLR) [122] and regulates the production of MAPK, AP-1 and NF-κB [123,124]. It also regulates the JAK/STAT signaling and reduces inflammatory responses by blocking the production of COX-2, iNOS, IFN-γ and lipoxygenase in NK cells [125–128]. Another way to reduce inflammation is by regulating inflammatory mediators such as interleukin-1 (IL-1), IL-17, IL-27, IL-6, IL-8, IL-1β [125,129]. Nuclear factor erythroid 2 p45-related factor (Nrf2) overactivation is seen in neoplasms [130]. A study has shown that curcumin could suppress protein Keap1, which interacts with Nrf2, thus regulating its overexpression. The transcription factor Nrf2 controls pathways involved in oxidative-stress defense. It is a potential target for treating chronic diseases [121,131].

In several preclinical studies, curcumin has shown positive effects on the reduction of inflammatory and catabolic markers in osteoarthritis rat models [132,133]. Other studies showed similar findings with an intraperitoneal injection of curcumin [134,135]. Oral administration of curcumin in rats with osteoarthritis show decreased serum levels of COX-2, 5-lipoxygenase and matrix metalloproteinase-3 (MMP-3) levels [136].

Clinical trials with curcumin have also shown promising results. Several studies have shown benefits on osteoarthritis pain following the administration of oral curcumin alone or as an adjunct [137–140]. Curcumin reduces prostaglandin E2 levels [141] and Coll2-1, a novel osteoarthritis marker, after curcumin administration [142]. Diseases studied include cancer, rheumatoid arthritis, neurological disorders, and cardiovascular and other inflammatory conditions.

Currently, over 250 studies on the therapeutic effects of curcumin are registered (https://www.clinicaltrials.gov/ct2/results?cond=&term=curcumin&cntry=&state=&city=&dist=). However, this shows that curcumin is still undergoing extensive clinical research.

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4.3. Quercetin

Quercetin is a flavonoid plant pigment chemically known as 2-(3,4-dihydroxyphenyl)3,5,7-trihydroxychromen-4-one. It belongs to the polyphenol family and is found in broccoli, tea, capers, berries, red onions, grapes and apples. Quercetin has many beneficial properties like anti-cancer, anti-inflammatory, antioxidant and anti-hyperglycemic actions [143].

Quercetin can inhibit eukaryotic translation by activating different kinases [144]. It scavenges ROS, inhibits the NF-κB, MAPK, STAT1 and the replication of many viruses [145–147]. Quercetin reduces the expression levels of COX-2 and NOS2 by suppressing AP-1 and STAT1 [148]. Administration of quercetin resulted in the inhibition of ICAM-1 expression in PMA endothelial cells [149] and in lung epithelial cells [150]. Quercetin decreases serum TNF-α, prostaglandin E2 (PGE2), IL-4, IL-5, and IFN-α levels in rodents [151,152]. Quercetin leads to reduced activation and migration of T cells by downregulating CD83 expression, downregulating immunoglobulin-like transcripts 3-5, ectonucleotidase of CD39 and CD73, and IL-12 [153]. Beneficial effects of quercetin have also been shown in rat studies [154–156]. Quercetin inhibits inflammation, oxidative stress and apoptosis in diabetic animals [157–159].

About 110 trials are registered at http://www.clinicaltrials.gov/ for quercetin. In addition, there are active, completed and recruiting trials (https://www.clinicaltrials.gov/ct2/results?cond=&term=quercetin&cntry=&state=&city=&dist=). They all study the effects of quercetin in inflammatory diseases, chronic obstructive pulmonary disease, diabetes, various types of cancer, cardiovascular diseases, children with Fanconi anemia, etc.

4.4. Capsaicin

Capsaicin is chemically known as (E)-N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methylnon-6-enamide. It is an alkaloid found in chili peppers (Solanaceae). In traditional medicine, this plant is a natural way to relieve pain in the joints and muscles and is an anti-irritant agent. After clinical trials, a capsaicin cutaneous patch has been approved by the European Union because of its effectiveness in neuropathic pain [160].

Capsaicin is an agonist for the transient receptor potential cation channel subfamily V member 1 (TRPV1) [161], which is a nonselective cation channel sensitized from noxious stimuli, leading to inflammatory conditions and pain [162]. Capsaicin activates and depolarizes TRPV1 receptors, initially causing a burning sensation. After the TRPV1 receptors are completely depolarized, the nociceptive areas are desensitized and reduce the pain signals in neurons [163,164].

A study has shown that capsaicin can reduce the iNOS, NF-κB, and COX-2 expression in macrophages [165]. There is one exception, which shows that capsaicin increases COX-2 in primary sensory neuron cells [166]. Capsaicin blocks activation of Jurkat cells [167] as well as proliferation in T leukemic cells [168] and in T cells in pancreatic lymph nodes [169]. In addition, it inhibits the production of TNF-α. It reduces the levels of IL-10, IL-4, and TGF-β1 [170].

About 311 trials are registered at http://www.clinicaltrials.gov/ for capsaicin (https://www.clinicaltrials.gov/ct2/results?cond=&term=capsaicin&cntry=&state=&city=&dist=). They all study the effects of capsaicin in chronic pain, various types of cancer, cardiac ischemia, osteoarthritis, rhinitis, etc.

4.5. Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is chemically known as [(2R,3R)-5,7-dihydroxy-2-(3,4, 5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl]3,4,5-trihydroxybenzoate]. EGCG has in vivo and in vitro chemoprotective, anti-oxidant, anti-angiogenic, anti-cancer and anti-inflammatory effects [171–174]. Studies have shown that EGCG blocked NF-κB activation by inhibiting IκBα [175,176] and also inhibited the proliferation of tumor cells and MAPK pathways [177,178].

EGCG has anti-apoptotic activity by reducing the expression of bax and caspase 3 [179–181]. Treatment with EGCG decreases TNF-α production [182], reduces serum IFN-γ, IL-17, IL-6, and IL-1β levels [183], attenuates activation of STAT3 to promote T cell responses [184] and may regulate

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epigenetic modifications of FoxP3, enhancing regulatory T cell responses [185]. EGCG inhibited the enzymes topoisomerase II, DNA methyltransferase and telomerase and affected DNA structure and function [186–188]. Treatment with EGCG also decreases the levels of MMP-9, iNOS, CCL-2, NADPH oxidase-4 mRNA etc. [189], but increase CD3, CD19, and Mac-3 which changes the number of B-, T-cells, and macrophages [190].

EGCG has been tested in different clinical trials. Over 100 clinical trials are registered for epigallocatechin-3-gallate alone or in combination with other substances (https://www.clinicaltrials.gov/ct2/results?cond=&term=Epigallocatechin-3-gallate&cntry=&state=&city=&dist=). They all study its effects on neurodegenerative diseases, Duchenne muscular dystrophy, chronic pain, cancer, obesity, acne, diabetes, etc.

4.6. Andrographolide

Andrographolide is chamicaly known as (3-[2-[decahydro-6-hydroxy-5-(hydroxymethyl)-5, 8-dimethyl-2-methylene-1-napthalenyl] ethylidene] dihydro- 4-hydroxy-2(3H)-furanone). Studies performed on the abilities of andrographolide to modulate the Wnt/β-Catenin, JAK-STAT, mTOR and VEGF/VEGFR signaling pathways are described [191]. They are all related to cancer progression, tumor growth or/and cancer activation and development.

Andrographolide decreases levels of TNF-α, IL-12, PGE2, COX-2, NO and iNOS in macrophages and microglia [192,193]. In addition, it regulates the IFN-γ, TNF-α, IL-2 and IL-6 production [194], reduces the proliferation of endothelial cells and the ICAM-1 adhesion molecule [195]. In 2011, Lee et al. showed that andrographolide downregulated iNOS and COX-2 by inhibiting the expression of NF-κB and STAT3 [196]. Antigrapholide activity and its potential therapeutic role have also been observed in diabetes, cardiovascular diseases, hyperlipidemia, hypertension, and obesity [197].

Only 20 clinical trials are found for andrographolide. Some trials are completed, others are unknown, and there are trials recruiting volunteers (https://www.clinicaltrials.gov/ct2/results?cond=&term=Andrographolide&cntry=&state=&city=&dist=). They all study the effects of andrographolide in migraine disorders, arthritis, rheumatoid, respiratory infection, cancer, etc.

4.7. Genistein

Genistein is a natural phytoestrogen and chemical known as 4,5,7-trihydroxyisoflavone. It is a compound found in soybeans and has various health benefits. It inhibited COX-2 and iNOS expression [198], induced apoptosis [199], regulates vascular function [200] and inhibited the expression of CD106 and CD62E adhesion molecules [201]. Genistein reduces the risk of neurodegenerative diseases, chronic colitis, rheumatoid arthritis, metabolic disorders, and diabetes [202–205].

Only 76 clinical trials are found for genistein. Although almost all of them are completed, there are several withdrawn and terminated, two active, and several still unknown (https://www.clinicaltrials.gov/ct2/results?cond=&term=Genistein+&cntry=&state=&city=&dist=). They all study the effects of genistein on different types of cancer, cardiovascular diseases, neurodegenerative diseases, asthma, osteopenia, etc.

4.8. Colchicin

Colchicine is the primary alkaloid of the Colchicum autumnale plant, and its chemical structure is N-[(7S)-1,2, 3,10-tetramethoxy-9-oxo-6,7-dihydro-5H-benzo(a)heptalen-7]-ylacetamide. Extensive research has been conducted on how it affects microtubule dynamics and damages it [206,207]. Over the past ten years, researchers have conducted several trials with colchicine that have shown positive outcomes in acute pericarditis [208,209]. Colchicine can be used for prevention in patients after radiofrequency ablation [210] and also for post-pericardiotomy syndrome prevention [211].

Colchicine has a dual role in T-cell immunity. First, it inhibits T cell activation by downregulating IL-2 expression [213] and can induce ovalbumin-induced T cell responses if used as

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an adjuvant [214]. It has also been found to activate erythroid 2-related factor 2 in hepatocytes, thereby impairing myeloid cell activation and their anti-inflammatory function [215].

Colchicine has anti-fibrotic effects and inhibits tubulointerstitial fibrosis by activation of Bcl-2 and suppression of caspase-3 [216]. A study shows that colchicine inhibits TGF-β1 activity [217], suppresses smooth muscle cell proliferation and increases cell apoptosis [218].

Colchicine has been approved by the FDA (Federal Drug Administration) as a drug for Mediterranean fever and acute gout flares [219].

About 242 clinical trials are found and registered for colchicine (https://www.clinicaltrials.gov/ct2/results?cond=&term=colchicine&cntry=&state=&city=&dist=). Its potential therapeutic effects continue to be actively investigated. Over 25 clinical trials that are currently recruiting are listed at http://www.clinicaltrials.gov/. They aim to study colchicine's effects on kidney diseases, myocardial infarction, cardiovascular diseases, inflammatory responses, gout, different types of cancer, diabetes, COVID-19 etc.

Table 2 below shows the mechanism of action of plant-derived immunomodulatory compounds/molecules for which there is data for registered clinical trials to December 2022 [220–240].

Table 2. Other selected plant-derived immunomodulatory compounds/molecules registered in https://www.clinicaltrials.gov/.

Chemical c compounds/molecules	**Mechanism**	**Clinical trials (number)**	**Reference**
Berberine	Regulate T- cells cytokines TNF-α, IL-2 and IL-4 production.	84	[220]
Piperine	Reduce IL-1β, IL-6, and TNF-α; regulate expression of COX-2, NOS-2, and NF-κB.	28	[221]
Xanthohumol	Inhibit NO production	10	[222]
Matrine	Reduced reactive oxygen species inflammatory mediators and myeloperoxidase and maleic dialdehyde activity	2	[223]

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Daidzein	Decreases TNF-α, IL-1β, MCP-1, NO, and iNOS	24	[224]
Luteolin	Reduce secretion of INF-γ, IL-6, COX-2 and ICAM-1 Block heat shock protein 90 activity.	18	[225]
Apigenin	Downregulate expression of IL-1α, TNF-α, IL-8, COX-2 and iNOS; Decreased response of Th1 and Th17 cells.	12	[226]
Nobiletin	Inhibit COX-2 and iNOS expression by blocking NF-κB and MAPK signaling	1	[227]
Baicalein	Inhibit expression of iNOS, COX-2, TNF-α, IL-1β, PGE_2, and TNF-α by regulating NF-κB and ER-dependent pathway.	1	[228,229]
Kaempferol	Reduce iNOS and COX-2 by suppressing STAT-1, NF-kappa B, and AP-1. Decrease expression of ICAM-1, VCAM-1 and MCP-1.	5	[224]
Rutin	Suppress production of TNF-α, IL-6. Activation of NF-κB and leukocyte migration.	34	[230]

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Puerarin	Inhibit NF-κB and activation of STAT3.	8	[231]
Thymoquinone	Inhibit IL-1β, TNF-α, MMP-13, COX-2, and PGE2, MAPK p38, ERK1/2, and NF-kBp65.	8	[232]
Piceatannol	Inhibit iNOS expression and NF-kB, ERK, and STAT3.	1	[233]
Shikonin	Inhibit NF-κB activity and Th1 cytokines expression and induce Th2 cytokines.	2	[234]
Oleanolic acid	Reduce the level of IL-1α, IL-6, and TNF-α and adenosine deaminase activity.	4	[235]
Triptolide	Inhibits lymphocyte activation, IL-2, iNOS, TNF-α, COX-2, IFN-γ, NF-kB, NFAT, and STAT3.	25	[235]
Celastrol	Inhibit IL-2, iNOS, TNF-α, COX-2, adhesion molecules and topoisomerase II.	2	[236]
Tetrandrine	Regulates ERK/NF-κB signaling and inhibits activation of mesangial cells	2	[237]
Apocynin	Inhibit NADPH oxidase and suppress pro-inflammatory cytokines, CD4+ and CD8+T cells production.	8	[239]
11-keto-β-boswellic acid	Decrease IL-1, IL-2, IL-4, IL-6, and IFN-γ	1	[240]

5. Conclusions

The immune system is modulated broadly and nonspecifically by medicinal herbs, including effects on various immune cells, including macrophages, NK cells, granulocytes, and T cells. Therefore, a deeper comprehension of the immunomodulatory functions of plants, their mechanisms of action, and phytoconstituents would allow us to pinpoint natural-source lead compounds to create innovative, secure immunomodulators that can strengthen existing therapies. Since a considerable amount of plant-based medicines have shown their therapeutic effect, we covered the therapeutic action of some of the more important and most frequently studied plant-based immunomodulators. Unfortunately, this area is still not fully explored, as many plant extracts and components are still very poorly researched. Further study and elucidation are also needed for the precise cellular and molecular mechanisms underlying their action.

There are some conducted clinical studies related to the immunomodulatory activity of plants and their components, but also some limitations that need to be overcome before they are safe and

effective for clinical use. For example, adequate/standard protocols for microbial contamination control, appropriate dosage and initiation stage of treatment/prevention should be implemented. In addition, it must be classified all immunomodulators of plant origin in specific classes according to the inherent risk according to the condition of the patients using the data from national registries, physicians and clinical trials. Another limitation is the low bioavailability of some of these substances and the cost optimization of their extraction. Production, delivery and quality control strategies must be improved before they reach people. This will ensure their safety and effectiveness for future clinical applications. If these obstacles are improved and overcome, their application will be very beneficial for preventing and managing chronic diseases

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