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S. Parchami Ghazaei, PhD of Biological Sciences, Associate Professor,
ORCID: [0000-0002-3829-3270](https://orcid.org/0000-0002-3829-3270),
sep_par_71@ukr.net

K. Marchenko-Tolsta, MD, Senior Lecturer,
ORCID: [0000-0001-7744-5874](https://orcid.org/0000-0001-7744-5874),

M. Zolotaikina, PhD of Pharmaceutical Sciences, Assistant,
ORCID: [0009-0007-8576-2176](https://orcid.org/0009-0007-8576-2176),

I. Tymchenko, PhD of Medical Sciences, Associate Professor,
ORCID: [0009-0000-0364-9639](https://orcid.org/0009-0000-0364-9639),

L. Novykova, MPharm, Senior lecturer,
ORCID: [0000-0001-5103-1016](https://orcid.org/0000-0001-5103-1016),

Y. Marchenko, MD,
ORCID: [0009-0006-9954-325x](https://orcid.org/0009-0006-9954-325x),
Smart Medical Center, Kyiv, Ukraine,

Kyiv Medical University, Kyiv, Ukraine,
Department of Pharmacology and Pharmacotherapy

PHARMACOLOGICAL MECHANISMS AND THERAPEUTIC IMPLICATIONS OF HERBAL IMMUNOMODULATORS (Mini-Review)

Abstract. Introduction. Immunomodulatory medicinal plants have been extensively investigated *in vitro*, in animal models, and in human studies. Aromatic and essential oil-containing species, including *Laurus nobilis*, *Nigella sativa*, *Withania somnifera*, *Echinacea purpurea*, and *Andrographis paniculata*, comprise bioactive phytochemicals such as terpenoids, flavonoids, and phenolic compounds that influence both innate and adaptive immune responses. **Aim of the study.** This review aimed to provide a translational analysis of mechanistic, preclinical, and clinical evidence supporting their immunomodulatory potential. **Methodology.** A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science, focusing on experimental and human studies reporting immunological outcomes. **Discussion.** Preclinical investigations demonstrate that plant-derived compounds modulate macrophage activation, cytokine expression, lymphocyte proliferation, and natural killer (NK) cell activity. For example, andrographolide influences T-cell signalling and cytokine production, while thymoquinone enhances NK cell cytotoxicity and regulates Th1/Th2 balance. Translational human studies report increased lymphocyte counts and cytokine levels following supplementation with standardised extracts. Randomised controlled trials further indicate that *Withania somnifera* enhances immunoglobulins, T helper cells, and NK cell activity. *Echinacea purpurea* increases NK cytotoxicity and cytokine production, and *Allium*-based formulations reduce the incidence and severity of respiratory infections in older adults. From a pharmacological perspective, these plants act as multi-target agents modulating signalling cascades and gene expression. However, variability in extract standardisation, dosage regimens,

and bioavailability contributes to heterogeneity in clinical outcomes. **Conclusion.** Overall, medicinal plants demonstrate regulatory rather than purely stimulatory immune effects, supporting their potential role in integrative immunotherapy. Further large-scale, well-controlled trials using standardised preparations are required to strengthen clinical translation.

Keywords: immunomodulation; cytokine; medicinal plants; phytochemicals.

INTRODUCTION

Immunomodulatory medicinal plants have been widely investigated using *in vitro* systems, animal models, and human clinical trials. Studies have evaluated both isolated bioactive compounds and standardised extracts. While experimental findings are substantial, it appears that comprehensive understanding of their therapeutic efficacy in large, well-controlled clinical settings remains limited [1, 2]. Several aromatic and essential oil-containing medicinal plants have been comprehensively reviewed regarding their phytochemical composition, immunomodulatory properties, safety, and toxicity profiles. These include bay laurel (*Laurus nobilis*), black cumin (*Nigella sativa*), clove (*Syzygium aromaticum*), fennel (*Foeniculum vulgare*), lemon balm (*Melissa officinalis*), lemongrass (*Cymbopogon citratus*), marjoram (*Origanum majorana*), peppermint (*Mentha piperita*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), and thyme (*Thymus vulgaris*) [3]. These plants comprise volatile terpenoids, phenolic compounds, and flavonoids that may influence innate and adaptive immune responses. Experimental studies suggest that these phytochemicals influence macrophage activation, cytokine production, lymphocyte proliferation, and natural killer cell activity, thereby contributing to immunoregulation [4]. However, variability in extraction procedures, phytochemical standardisation, and dosage regimens limits direct comparison across studies and complicates interpretation of clinical efficacy. To provide a structured analysis, the following section presents evidence in a translational sequence, beginning with mechanistic and preclinical investigations, and subsequently addressing translational human studies and randomised clinical trials.

METHODOLOGY

For this review, a comprehensive literature search was conducted using electronic databases, including PubMed, Scopus, and Web of Science, focusing on studies published up to 2025. Keywords included “medicinal plants,” “immunomodulation,” “phytochemicals,” “preclinical studies,” “clinical trials,” “cytokines,” “natural killer cells,” and the Latin names of commonly used herbs. Both experimental (*in vitro*, *in vivo*) and human studies were considered. Selection criteria prioritised studies reporting immunological outcomes, mechanistic insights, or translational relevance, with particular attention to standardised extracts, isolated bioactive compounds, and safety profiles. Data were extracted regarding phytochemical composition, immunomodulatory effects, dosage, administration route, and observed adverse effects.

DISCUSSION

Preclinical and Mechanistic Evidence

In animal models of cyclophosphamide-induced immunosuppression, *Andrographis paniculata*, a traditional herb and member of the Acanthaceae family widely utilised in Ayurveda and traditional Chinese medicine, restored thymus architecture, improved the macrophage phagocytic index, and enhanced both humoral and delayed-type hypersensitivity responses. Andrographolide, the principal

diterpenoid lactone, has been shown to modulate T-cell activation and cytokine expression, including IFN- γ and IL-2 [5]. Extending these findings, preclinical studies demonstrated that oral administration of *A. paniculata* extract at 250 and 500 mg/kg for 15 days in cyclophosphamide-immunosuppressed mice enhanced macrophage phagocytic activity, restored normal thymic architecture, and significantly improved both humoral and delayed-type hypersensitivity responses [6].

Experimental studies on *Nigella sativa* demonstrated that thymoquinone increases natural killer cell cytotoxicity and antibody production in murine models. Modulation of Th1/Th2 cytokine balance has also been observed, suggesting a regulatory role in immune homeostasis [7]. Additionally, in a pristane-induced lupus mouse model, *Nigella sativa* treatment significantly reduced expression of proinflammatory cytokines (IL17, IL6, IL23) and mitigated renal tissue damage while enhancing regulatory T cell populations, further confirming its immunomodulatory capacity [8].

Translational Human Investigations

Translational studies provide preliminary evidence of immunomodulatory effects in humans, although methodological limitations must be considered.

A 30-day open-label study evaluating standardised extract of *Andrographis paniculata* demonstrated significant increases in total lymphocyte count, CD3⁺ and CD4⁺ T cells, and IFN- γ levels. IL-2 exhibited a biphasic response, increasing at day 7 and decreasing by day 30, potentially reflecting modulation of regulatory T-cell activity. No adverse events were reported, supporting favourable tolerability [9]; however, the absence of placebo control limits definitive conclusions.

Evidence from Randomised Controlled Clinical Trials

Ashwagandha (*Withania somnifera*, WS) is a prominent Rasayana remedy in the Ayurvedic tradition of India. In line with its traditional use, a randomised, double-blind, placebo-controlled study demonstrated that 30 days of supplementation with a 180 mg capsule—containing 60 mg of WS extract standardised to 21 mg of withanolide glycosides—significantly enhanced immune parameters in healthy individuals. The treatment led to a statistically significant increase ($p < 0.05$) in immunoglobulins, T helper cells, cytokines (IFN- γ , IL-4), natural killer cells, and B lymphocytes. Together, these results suggest that WS may serve as a promising immunomodulatory agent, potentially benefiting adults, including older adults, as well as providing protection during periods of widespread infection [10].

Similarly, results of a randomised, double-blind, placebo-controlled clinical trial demonstrated that daily administration of 200 mg *Echinacea purpurea* extract for 8 weeks led to a marked increase in natural killer cell cytotoxicity and upregulation of serum cytokines, especially IL-2, IFN- γ , and TNF- α . Moreover, no adverse events or clinically relevant changes in laboratory parameters were observed, confirming the safety of the plant and supporting its efficacy as a potential immunomodulator in humans [11].

In agreement with earlier reports, a randomised, double-blind, placebo-controlled trial conducted by García-García et al. evaluated the prophylactic efficacy of a phytotherapeutic formulation against respiratory infections in healthy older adults residing in nursing homes, the majority of whom were over 80 years of age. Over a 36-week period, participants were administered either a placebo or a preparation containing standardised onion extract, garlic powder (*Allium spp.*), and microcrystalline cellulose. A significantly lower incidence of respiratory infections, including influenza and the common cold, was observed in the intervention group compared to controls. In addition, the frequency and severity of symptoms such as cough, fatigue, and dyspnoea were markedly reduced, with individuals in the placebo group being more than 3.5 times as likely to report symptoms during the study period. Collectively, these findings suggest that *Allium*-derived phytochemicals may offer synergistic protective effects and serve as a promising immune-supportive strategy in ageing populations [12]. Preclinical and clinical findings on selected herbal immunomodulators are summarised in Table 1.

Pharmacological Perspectives on Plant-Derived Immunomodulators

From a pharmacological standpoint, medicinal plants with immunomodulatory properties function as multi-target agents acting on both innate and adaptive immune pathways. Unlike single-molecule synthetic drugs, phytochemicals typically exert pleiotropic effects through modulation of signalling cascades, cytokine networks, and immune cell differentiation [13]. Pharmacodynamically, extracts of *Withania somnifera* have been associated with regulation of NF-κB-mediated gene expression, influencing production of pro- and anti-inflammatory cytokines [14]. Constituents of *Echinacea purpurea* may interact with cannabinoid receptor type 2 (CB2), thereby modulating immune cell activation [15]. Diterpenoid lactones from *Andrographis paniculata* appear to influence T-cell signalling and cytokine expression [16], while organosulfur compounds from *Allium sativum* regulate inflammatory gene transcription and macrophage activity [17].

Table 1. Preclinical and clinical findings on selected herbal immunomodulators

Plant	Study Type	Model / Population	Main Immunological Effects
<i>Andrographis paniculata</i>	Preclinical	Cyclophosphamide-induced immunosuppressed mice	↑ Macrophage phagocytic activity; improved humoral and delayed-type hypersensitivity responses; restoration of thymus architecture
<i>Nigella sativa</i>	Preclinical	Murine models; pristane-induced lupus model	↑ NK cell cytotoxicity; ↑ antibody production; ↓ IL-17, IL-6, IL-23; ↑ regulatory T cells
<i>Withania somnifera</i>	RTC	Healthy adults	↑ Immunoglobulins; ↑ T helper cells; ↑ IFN-γ, IL-4; ↑ NK cells; ↑ B lymphocytes
<i>Echinacea purpurea</i>	RTC	Healthy adults	↑ NK cell cytotoxicity; ↑ IL-2, IFN-γ, TNF-α
<i>Allium</i> -based phytochemicals (e.g., <i>Allium sativum</i>)	RTC	Older adults (>80 years) in nursing homes	↓ Incidence and severity of respiratory infections

Note: RTC, Randomised Controlled Trial; NK, Natural killer.

Source: created by the authors.

Pharmacokinetic (PK) considerations are equally relevant. The bioavailability of phytoconstituents such as withanolides and andrographolide may be influenced by intestinal absorption, hepatic metabolism, and microbial biotransformation within the gut. Variability in extract standardisation and interindividual metabolic differences may therefore contribute to heterogeneity in clinical outcomes [18].

A biphasic dose–response has been reported for several plant-derived compounds across multiple studies. Although these phytochemicals exhibit adaptive immunological effects, their clinical application is limited by issues of bioavailability and dosage standardisation [19].

From a clinical pharmacology perspective, safety and interaction profiles require careful evaluation. A thorough understanding of the PK characteristics of bioactive plant compounds is essential for predicting potential herb–drug interactions, particularly through modulation of drug-metabolizing enzymes, transporters, and intestinal barrier integrity [20].

CONCLUSION

Across experimental and clinical studies, common immunological patterns emerge. Many medicinal plants enhance NK cell activity, modulate Th1/Th2 cytokine balance, increase lymphocyte proliferation,

and elevate immunoglobulin levels. Rather than exerting uniform immune stimulation, several phytocompounds appear to promote immune regulation and homeostasis.

However, variability in extract standardisation, modest sample sizes, and limited long-term safety data remain important limitations. Future investigations should prioritise standardised preparations, mechanistic clarification, and large-scale clinical trials to strengthen translational relevance within integrative phytotherapy.

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Фармакологічні механізми та терапевтичні імплікації рослинних імуномодуляторів (міні-огляд)

С. Парчамі Газеає, кандидат біологічних наук, доцент,

ORCID: 0000-0002-3829-3270,

sep_par_71@ukr.net

К. Марченко-Толста, старший викладач,

ORCID: 0000-0001-7744-5874,

k.marchenko-tolsta@kmu.edu.ua

М. Золотайкіна, кандидат фармацевтичних наук, асистент

ORCID: 0009-0007-8576-2176,

m.zolotaikina@kmu.edu.ua

І. Тимченко, кандидат медичних наук, доцент,

ORCID: 0009-0000-0364-9639,

i.tymchenko@kmu.edu.ua

Л. Новикова, старший викладач,

ORCID: 0000-0001-5103-1016,

l.novikova@kmu.edu.ua

Ю. Марченко, гінеколог,

ORCID: 0009-0006-9954-325x,

Смарт Медікал Центр, Київ, Україна,

y.marchenko@kmu.edu.ua

Київський медичний університет, Київ, Україна,

Кафедра фармакології та фармакотерапії

Анотація. Вступ. Лікарські рослини з імуномодулюючими властивостями широко досліджені *in vitro*, на тваринних моделях та у дослідженнях за участю людей. Ароматичні та ефірні олії, включаючи *Laurus nobilis*, *Nigella sativa*, *Withania somnifera*, *Echinacea purpurea* та *Andrographis paniculata*, містять біоактивні фітохімічні речовини, такі як терпеноїди, флавоноїди та фенольні сполуки, які впливають як на вроджені, так і на адаптивні імунні відповіді. Мета цього огляду – надати трансляційний аналіз механістичних, доклінічних та клінічних доказів, що підтверджують їхній імуномодулюючий потенціал. **Методологія.** Проведено комплексний пошук літератури з

використанням PubMed, Scopus та Web of Science, зосереджуючись на експериментальних та людських дослідженнях, що повідомляють про імунологічні результати. **Обговорення.** Доклінічні дослідження демонструють, що сполуки рослинного походження модулюють активацію макрофагів, експресію цитокінів, проліферацію лімфоцитів та активність природних клітин-кілерів (NK). Наприклад, андрографолід впливає на сигнальні шляхи T-клітин та продукцію цитокінів, тоді як тимохінон посилює цитотоксичність NK-клітин та регулює баланс Th1/Th2. Трансляційні клінічні дослідження повідомляють про підвищення кількості лімфоцитів та рівня цитокінів після застосування стандартизованих екстрактів. Рандомізовані контрольовані дослідження також свідчать, що *Withania somnifera* підвищує рівні імуноглобулінів, активність T-хелперів та NK-клітин. *Echinacea purpurea* збільшує цитотоксичність NK-клітин та продукцію цитокінів, а препарати на основі *Allium* знижують частоту та тяжкість респіраторних інфекцій у людей похилого віку. З фармакологічної точки зору, ці рослини діють як багатоцільові агенти, що модулюють сигнальні каскади та експресію генів. Однак, мінливість у стандартизації екстракту, режимах дозування та біодоступності сприяє гетерогенності клінічних результатів. **Висновок.** Загалом, лікарські рослини демонструють скоріше регуляторні, ніж суто стимулюючі імунні ефекти, що підтверджує їхню потенційну роль в інтегративній імунотерапії. Для посилення клінічної трансляції необхідні подальші масштабні, добре контрольовані клінічні дослідження з використанням стандартизованих препаратів.

Ключові слова: імуномодуляція; цитокін; лікарські рослини; фітохімічні речовини.

Автори заявляють про відсутність конфлікту інтересів. [The authors declare no conflict of interest.]

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