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REVIEW ARTICLE

A Systematic Review of the Immunomodulatory Effects and Therapeutic Applications of *Withania somnifera, Tinospora cordifolia, Cinnamomum zeylanicum,* and *Piper longum*: Underlying Mechanisms and Clinical Significance

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Abstract

The growing awareness of emerging health risks has driven an increased emphasis on wellness and proactive health strategies that bolster resistance to illness. Health-conscious individuals are progressively turning to natural remedies, including traditional medicines, as a complementary approach to a balanced diet and regular exercise for immune system enhancement. Immunomodulators, encompassing both natural and synthetic agents, influence immune function to produce therapeutic effects. These effects may manifest as immune stimulation, restoration of immune homeostasis, suppression of excessive responses, or enhancement of immune activity via adjuvants. This review explores the immunomodulatory potential of *Withania somnifera* (L.) Dunal, *Tinospora cordifolia* (Willd.) Miers, *Cinnamomum zeylanicum* Blume (synonym: *Cinnamomum verum* J.Presl), and *Piper longum* L., focusing on their ethnomedicinal applications, phytochemical profiles, pharmacological activities, and safety parameters. *W. somnifera (Ashwagandha)*, a cornerstone of *Ayurvedic* medicine, is renowned for its immunomodulatory, anticancer, and neuroprotective properties. Similarly, *T. cordifolia (Guduchi)*, an Indian climbing shrub, is extensively utilised for its antiperiodic, anti-inflammatory, antidiabetic, and immunostimulatory effects in the management of various disorders. The bark of *C. zeylanicum (Dalchini)*, commonly used as a culinary spice, is traditionally employed for its ability to alleviate vomiting, flatulence, diarrhoea, and haemorrhages. *P. longum (Pippali)*, a climbing plant, holds significant therapeutic value for conditions such as respiratory infections, bronchitis, diarrhoea, and spleen disorders. **Major Findings:** This review examines the phytochemistry and immunomodulatory-antioxidant roles of *W. somnifera*, *T. cordifolia*, *C. zeylanicum*, and *P. longum*. Their bioactives regulate cytokines, reduce oxidative stress, and activate immune cells. These actions underline their potential in treating immune disorders and enhancing host defence.

Keywords: *Ashwagandha, Dalchini, Guduchi,* Immune Homeostasis, Immune Suppressants, Immunomodulators, *Pippali,* Traditional Medicines

1. Introduction

In traditional Indian medicine systems, particularly *Ayurveda*, a wide variety of herbal and mineral-based preparations have been employed for centuries to manage an extensive range of human diseases and conditions. *Ayurveda*, among the oldest documented medical systems, traces its origins to around 6000 BCE and has been extensively practised in India and Sri Lanka. This ancient system emphasises holistic health and relies on herbal and herbo-mineral formulations rooted in specific diagnostic, therapeutic, and

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preventive principles. A key aspect of *Ayurveda* is its focus on immunomodulation, a concept that has drawn significant scientific interest due to its potential to enhance health and resilience. Central to this principle is the *Ayurvedic* concept of *Rasayana*, which emphasises rejuvenation, promoting longevity, and fortifying the body's immune defences. *Rasayana* therapy is believed to enhance *Ojas*, the vital energy associated with immunity and well-being. Numerous plants have been traditionally utilised for their immunomodulatory properties, demonstrating the ability to regulate and fine-tune immune responses. Immunomodulators, whether derived naturally or synthetically, are substances that modify immune activity by influencing the magnitude, type, or duration of immune responses. Key mechanisms of immunomodulation include enhancing chemotaxis, phagocytosis, and the production of cytokines, which are critical mediators of immunity. Notable *Ayurvedic* plants such as *W. somnifera (Ashwagandha), T. cordifolia (Guduchi), C. zeylanicum (Dalchini), and P. longum (Pippali)* have been widely studied for their ability to support these immune mechanisms[1]. The selection of these four medicinal plants is based on their complementary and synergistic immunomodulation, as these plants exhibit immunostimulatory and immunoregulatory properties via distinct but complementary pathways, including cytokine modulation, antioxidant defence, and adaptogenic effects. They also possess *ayurvedic* and ethnopharmacological relevance as they are key components of traditional formulations used for immune enhancement, aligning with both historical use and modern pharmacological validation. A preliminary literature survey identified these plants as having substantial preclinical and clinical evidence supporting their immunomodulatory effects, making them suitable candidates for a focused review, along with significant translational potential, as, unlike isolated plant reviews, our work aims to provide a comprehensive framework for their clinical applicability in immune-related disorders.

For instance, *W. somnifera*, known for its adaptogenic properties, modulates immune function by reducing oxidative stress and improving cell-mediated immunity. *T. cordifolia*, rich in alkaloids and glycosides, is reported to stimulate macrophage activity and improve resistance to infections. *C. zeylanicum* exhibits anti-inflammatory and antioxidant activities, which contribute to immune regulation, while *P. longum* enhances immune surveillance through its alkaloid-rich profile. True immunomodulation, as observed in these botanicals, involves the dual capacity to activate immune responses under conditions of immunosuppression while suppressing hyperactive immunity in conditions such as allergies and autoimmune diseases. Beyond their immune-specific roles, these plants often exert pleiotropic effects, such as regulating oxidative stress, supporting gut health, and modulating the neuroendocrine axis, thereby contributing to overall homeostasis. Such multifaceted actions highlight their potential as integrative therapeutic agents in modern medicine[2].

2. Materials and Methods

The article published in Google Scholar, PubChem, AYUSH research portal, PubMed.gov research online portal were analysed for this review article. The keywords used for database search include "*W. somnifera, T. cordifolia, C. zeylanicum, P. longum, Immunomodulation* and *Antioxidant activity*". Only articles published in English were included in this review. No other exclusion criteria were applied regarding journal, years, authors, *etc*. A comprehensive list of all articles published until September 2024 was prepared. In the next stage, all the articles obtained from searching the databases were compiled and screened by reading their "title" and then the "abstract." Studies that satisfied the inclusion criteria, i.e. immunomodulator, antioxidant, cytokine pathways and macrophage activity studies, were only included at this stage and others were excluded. The selected articles were finally screened by reading the full-text or abstract, as per availability and were analysed further.

3. Immune System

The immune system plays a fundamental role in maintaining the body's integrity by identifying and eliminating non-self entities, such as pathogens and abnormal cells. This complex defence mechanism operates through a highly coordinated network of cellular and humoral components dispersed throughout the body. By recognising and responding to foreign

substances and organisms, the immune system serves as a critical interface between health and disease, ensuring the host's survival and well-being. The immune system is composed of numerous interdependent cell types that work synergistically to defend against bacterial, parasitic, fungal, and viral infections, as well as to inhibit the progression of tumour cells. These immune cells exhibit specialised functions tailored to specific threats. For instance, macrophages and neutrophils engulf and digest bacteria through phagocytosis, while Natural Killer (NK) cells and cytotoxic T-lymphocytes target and destroy virus-infected or malignant cells (Figure 1). Eosinophils play a pivotal role in combating parasitic infections, and dendritic cells serve as antigen-presenting cells to initiate adaptive immune responses. A key component of immune function lies in the activation and coordination provided by T-helper (Th) cells, a subset of T-lymphocytes. These cells orchestrate immune responses by secreting signalling molecules collectively known as cytokines. Cytokines, including lymphokines and interleukins, act as chemical messengers that regulate the activity, differentiation, and proliferation of various immune cells. Depending on the type of immune response required, Th cells polarise into distinct subsets such as Th1, Th2, Th17, or regulatory T-cells, each secreting specific cytokines to direct appropriate immune responses. Through these multifaceted mechanisms, the immune system maintains a delicate balance between tolerance and defence, ensuring effective responses to harmful agents while avoiding damage to the host's tissues. Dysregulation of this system can lead to immune deficiencies, hypersensitivity reactions, or autoimmune disorders, emphasising the critical need for precise immune regulation[2].

4. Disorders of Human Immunity

The immune system is an intricately designed defence network characterised by its specificity, inducibility, and adaptability. It is capable of recognising and responding to a diverse array of pathogens and abnormal cells with remarkable precision. Despite its efficiency, failures in host defence can occur, leading to dysfunction in immune responses. These failures are generally classified into three broad

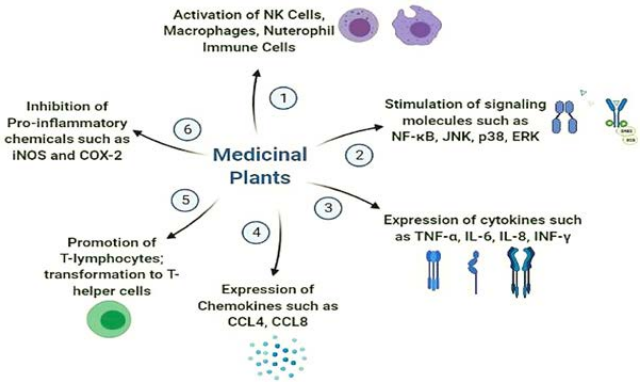


Figure 1. Types of Immuno-stimulatory Mechanisms triggered by medicinal plants[3].

categories: immunodeficiencies, autoimmunity, and hypersensitivities[2].

4.1 Immunodeficiency

Immunodeficiency occurs when one or more critical components of the immune system are compromised or inactive, leading to a reduced ability to defend against infections and other immune challenges. In developing countries, malnutrition is the most prevalent cause of immunodeficiency. Diets deficient in essential nutrients, particularly proteins, are strongly associated with impaired immune function. Protein deficiency affects various aspects of immunity, including cell-mediated immunity, complement activity, phagocytic function, the concentration of IgA antibodies, and cytokine production, all of which are essential for effective immune responses. Moreover, deficiencies in key micronutrients such as zinc, selenium, iron, copper, and vitamins including A, C, E, and B6, as well as folic acid (vitamin B9), have been shown to significantly diminish immune function. These nutrients are vital for maintaining the integrity and activity of immune cells, influencing cellular signalling, and supporting antioxidant defences, which are critical in combating infections and inflammation. Immunodeficiencies can be categorised into two main types: primary (inherited) and secondary (acquired). Primary immunodeficiencies are genetic disorders that impair the development or function of immune cells, often manifesting in childhood. Secondary immunodeficiencies, on the other hand, result from external factors such as infections (*e.g.*, HIV), malnutrition, or immunosuppressive

treatments, and they can affect individuals at any age (Figure 2). Understanding the role of nutrition and nutrient deficiencies in immune system functionality is crucial, as improving dietary intake can significantly enhance immune responses and reduce susceptibility to infections and diseases[2,4].

4.2 Autoimmunity

Autoimmune diseases occur when the immune system mistakenly targets and attacks the body's tissues, failing to recognise self-antigens as distinct from foreign invaders. This breakdown in immune tolerance leads to chronic inflammation and tissue damage. Normally, the immune system is capable of distinguishing between self and non-self entities through processes like central and peripheral tolerance, but in autoimmune conditions, this system of checks and balances is disrupted. Common examples of autoimmune diseases include rheumatoid arthritis, in which the immune system attacks the synovial joints, leading to inflammation, pain, and eventual joint destruction (Figure 3). Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disorder that affects multiple organ systems, including the skin, kidneys, and cardiovascular system, often causing chronic inflammation and tissue damage. Multiple Sclerosis (MS) occurs when the immune system attacks the protective sheath of nerve fibres in the central nervous system, leading to neurological impairment. Insulin-dependent diabetes mellitus (Type 1 diabetes) arises when the immune system destroys insulin-producing beta cells in the pancreas, resulting in insulin deficiency and impaired glucose regulation. The exact causes of autoimmune diseases are not fully understood, but they are believed to result from a complex interplay of genetic susceptibility, environmental factors (such as infections, toxins, or dietary factors), and immune dysregulation. Genetic variations may predispose individuals to autoimmune diseases, and environmental triggers may activate the immune system, leading to disease onset. These diseases represent a failure of the immune system to maintain self-tolerance, and they often involve autoantibodies or autoreactive T cells that target the body's tissues. Advances in understanding the molecular mechanisms behind autoimmune diseases are critical for developing targeted therapies that can modulate immune responses without compromising overall immunity[4].

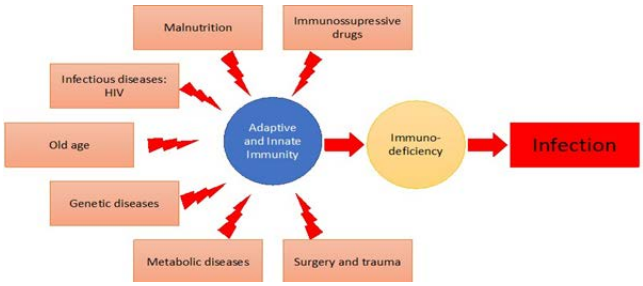


Figure 2. Different causes of immunodeficiency[5].

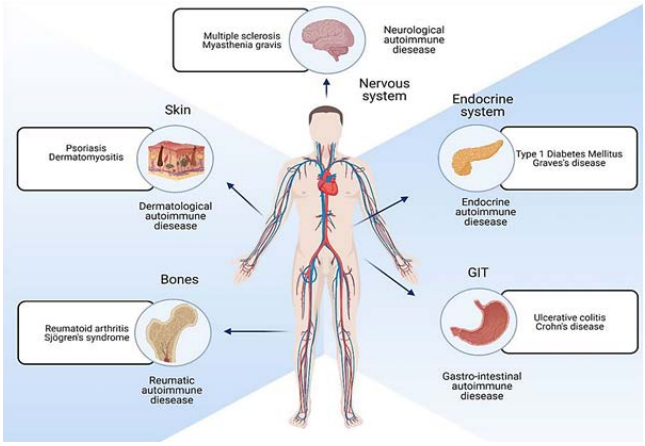


Figure 3. Types of autoimmune diseases[6].

4.3 Hypersensitivities

Hypersensitivity refers to an exaggerated or inappropriate immune response to harmless substances, such as allergens or environmental factors. It can be classified into two main categories based on the underlying immune mechanism: antibody-mediated and cell-mediated hypersensitivity. Types I through III hypersensitivity reactions are antibody-mediated (Figure 4), involving immunoglobulins (IgE, IgG, or IgM) that trigger inappropriate immune responses. Type I hypersensitivity (immediate or allergic reactions) involves IgE antibodies, which bind to mast cells and basophils, leading to the release of histamine and other mediators upon subsequent antigen exposure. Examples include asthma, allergic rhinitis, and anaphylaxis. Type II hypersensitivity (cytotoxic reactions) involves IgG or IgM antibodies directed against antigens on cell surfaces, leading to cell destruction through complement activation or phagocytosis. An example is autoimmune haemolytic anaemia. Type III hypersensitivity (immune complex-mediated reactions) occurs when antigen-antibody complexes deposit in tissues, triggering inflammation

and tissue damage, as seen in conditions like systemic lupus erythematosus (SLE) and rheumatoid arthritis. Type IV hypersensitivity, on the other hand, is cell-mediated, involving T lymphocytes rather than antibodies. In this reaction, CD4+ helper T cells or CD8+ cytotoxic T cells become activated against an antigen, leading to tissue inflammation and damage. This type of hypersensitivity is seen in contact dermatitis, tuberculin reactions, and graft-versus-host disease. Hypersensitivity reactions unfold in two distinct phases: the sensitisation phase and the effector phase. During the sensitisation phase, the immune system encounters the antigen for the first time. In antibody-mediated types, the immune system produces specific antibodies (*e.g.*, IgE in Type I) or immune complexes (in Types II and III). In cell-mediated reactions, T cells become activated. Sensitisation does not produce immediate symptoms but primes the immune system for future encounters. The effector phase occurs upon re-exposure to the antigen, during which immune memory is activated, resulting in a rapid and amplified immune response. This phase leads to tissue inflammation and pathology, often causing clinical symptoms such as swelling, pain, and tissue damage. Understanding the phases and mechanisms of hypersensitivity reactions is essential for developing therapeutic interventions to manage allergic, autoimmune, and inflammatory disorders effectively[4,7].

5. The Role of *Ayurveda* in Immunomodulation and Antioxidant Activity

Ayurveda, the ancient Indian system of medicine, highlights the significance of maintaining a balanced immune system and harnessing the body's natural defences against disease. *Ayurvedic* remedies, crafted from herbs, minerals, and animal-derived substances, are pivotal in supporting immunomodulation and boosting antioxidant activity.

5.1 Immunomodulation in *Ayurveda* – The Role of Key Herbs

In *Ayurvedic* medicine, the immune system is viewed as an intricate network that sustains health by balancing the three *Doshas* — *Vata, Pitta, and* Kapha — and nurturing *Ojas*, the vital essence of immunity and vitality. Immunomodulation, as understood in *Ayurveda*, involves restoring and maintaining this balance to strengthen the body's defence mechanisms while preserving homeostasis. This holistic approach integrates dietary practices, lifestyle modifications, and herbal therapies, emphasising the use of *Rasayana* — rejuvenative agents.

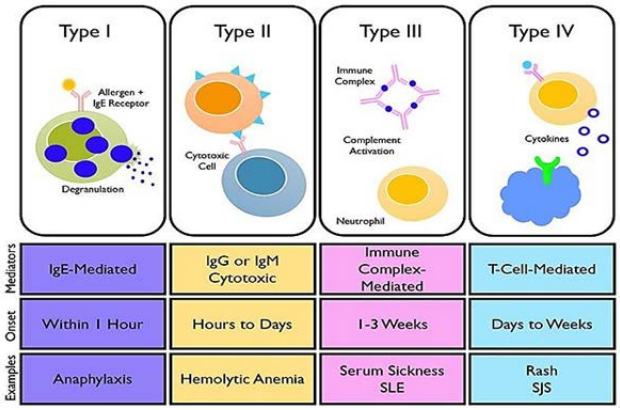


Figure 4. Types of hypersensitivity reactions[8].

Several *Ayurvedic* herbs have demonstrated potent immunomodulatory activity, with scientific evidence now substantiating their traditional uses. Among these, *W. somnifera* (*Ashwagandha*), *T. cordifolia* (*Guduchi*), *C. zeylanicum* (Dalchini), and *P. longum* (Pippali) hold a prominent position. These plants possess diverse bioactive compounds that contribute to their ability to regulate immune responses, combat oxidative stress, and promote overall well-being[7,9].

5.1.1 *W. somnifera* (L.) Dunal (Ashwagandha)

Withania somnifera, known as *Ashwagandha* in *Ayurveda*, is a revered *Rasayana* herb renowned for its adaptogenic, immunomodulatory, and neuroprotective properties. The root contains bioactive compounds like withanolides, which have been shown to enhance immune function by promoting the proliferation of immune cells and modulating cytokine production. *Ashwagandha*'s ability to reduce stress-induced immune suppression further highlights its role in maintaining immune homeostasis.

In *Ayurveda*, *Ashwagandha* (Figure 5) is traditionally used to strengthen *Ojas*, rejuvenate the body, and combat fatigue and stress, which are known to weaken immunity. Modern studies corroborate its effectiveness

in enhancing phagocytic activity and restoring immune responses in immunocompromised conditions[10].

5.1.2 *T. cordifolia (Willd.) Miers (Guduchi)*

Tinospora cordifolia, or *Guduchi*, is another cornerstone of *Ayurvedic* immunomodulation. Known for its *Rasayana* properties, *Guduchi* (Figure 6) is rich in alkaloids, diterpenoids, and glycosides, which contribute to its immune-enhancing, anti-inflammatory, and antipyretic effects. It enhances chemotaxis, phagocytosis, and T-cell proliferation, key components of the immune response.

Ayurvedic texts describe *Guduchi* as "*Amrita*" (nectar) due to its ability to support longevity and resilience. Its role in modulating both innate and adaptive immunity makes it particularly effective in combating infections, managing inflammatory disorders, and restoring immune balance in autoimmune conditions[12].

5.1.3 *C. zeylanicum Blume (synonym: C. verum J.Presl) (Dalchini)*

The bark of *C. zeylanicum* is traditionally used in *Ayurveda* for its warming, digestive, and antimicrobial properties. Rich in cinnamaldehyde, eugenol, and flavonoids, cinnamon exhibits antioxidant, anti-inflammatory, and immunomodulatory activities.

Research indicates that cinnamon helps regulate immune responses by modulating cytokine production and inhibiting inflammatory pathways. Its antimicrobial properties further aid in defending the body against bacterial, fungal, and viral infections. In *Ayurveda*, *Daalchini* (Figure 7) is also valued for its ability to balance *Kapha* and promote digestion, indirectly supporting immunity[14].



Figure 5. **(a)** *W. somnifera* plant[11] **(b)** *W. somnifera* root, stem and leaves.



Figure 6. **(a)** *T. cordifolia* plant[13], **(b)** *T. cordifolia* stem and leaves.



Figure 7. **(a)** *C. zeylanicum* twig[15], **(b)** *C. zeylanicum* bark, stem and leaves.

5.1.4 *P. longum L. (Pippali)*

P. longum, or *Pippali*, is a powerful immunomodulator traditionally used to treat respiratory and digestive ailments. Its bioactive compounds, including piperine and essential oils, enhance the body's immune defences through anti-inflammatory, antimicrobial, and antiviral activities.

Pippali (Figure 8) is particularly effective in managing conditions such as cough, cold, and fever, where immune modulation is essential. It is also noted for its ability to enhance the bioavailability of other herbal constituents, thereby potentiating the effects of *Ayurvedic* formulations. *Pippali's* role in strengthening *Agni* (digestive fire) contributes to its overall immunomodulatory potential, as *Ayurveda* links a robust digestive system to strong immunity[16].

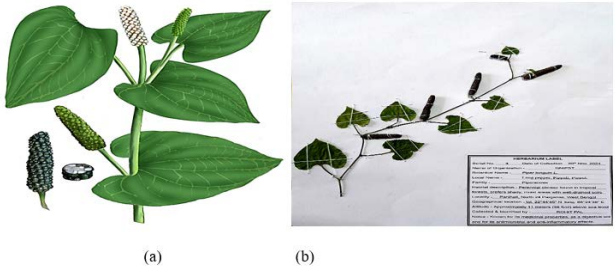
5.2 Integrated Immunomodulation in *Ayurveda*

The synergistic use of *W. somnifera*, *T. cordifolia*, *C. zeylanicum*, and *P. longum* in *Ayurvedic* formulations offers a comprehensive approach to immunomodulation. Together, these herbs:

- Enhance innate and adaptive immune responses.
- Regulate the production of pro-inflammatory and anti-inflammatory cytokines.
- Combat oxidative stress through potent antioxidant activity.
- Support the maintenance of *Dosha* balance and the enhancement of *Ojas*.

This integrative approach not only boosts immunity but also addresses the underlying factors contributing to immune dysregulation, such as stress, poor digestion, and *Dosha* imbalance[18].

Ayurvedic immunomodulation revolves around maintaining harmony within the body's systems to ensure optimal immune function. Central to this concept are the following principles (Depicted in Table 1).



(a) (b)

Figure 8. **(a)** *P. longum* plant[17], **(b)** *P. longum* leaves and fruits.

5.3 Immunomodulatory Herbs and Their Mechanisms

5.3.1 *W. somnifera (L.) Dunal (Ashwagandha)*

Ashwagandha enhances immune responses by modulating cytokines, increasing T-cell and B-cell activity, and boosting phagocytic function. Its adaptogenic properties lower cortisol levels, preventing stress-induced immune suppression and maintaining immune balance.

5.3.2 *T. cordifolia (Willd.) Miers (Guduchi)*

Guduchi activates macrophages and T-cells, promoting innate and adaptive immunity. It also regulates cytokine production and combats oxidative stress through its antioxidant compounds, supporting immune restoration in immunocompromised states.

5.3.3 *C. zeylanicum Blume (synonym: C. verum J. Presl) (Dalchini)*

Cinnamon reduces inflammation by inhibiting NF-κB and modulating cytokine levels. Its antimicrobial and

Table 1. Key concepts in *Ayurvedic* immunomodulation[18,19]

Sl. No.	Key Concepts	Immunomodulation
1	Balance of *Doshas*	*Ayurveda* emphasizes the balance of the three *Doshas—Vata, Pitta*, and *Kapha*—which represent different physiological energies. An imbalance in these *Doshas* disrupts immunity, and restoring their equilibrium strengthens the body's defenses.
2	*Ojas*	*Ojas*, considered the essence of vitality and immunity, is the ultimate product of perfect digestion and metabolism (*Agni*). It governs the body's ability to resist diseases, with depleted *Ojas* leading to immune weakness and susceptibility to illnesses.
3	*Rasayana* Therapy	*Rasayana* treatments aim to rejuvenate the body, enhance vitality, and strengthen immunity. Herbs classified as *Rasayana*, such as *Withania somnifera* and *Tinospora cordifolia*, act as immunomodulators, restoring balance and boosting resistance to diseases.
4	*Agni* (Digestive Fire)	A well-functioning digestive system (*Agni*) is foundational to health and immunity in *Ayurveda*. Impaired digestion produces toxins (*Ama*), which weaken immunity, while a strong Agni ensures optimal nutrient absorption and immune function.
5	*Srotas* (Body Channels)	*Ayurvedic* immunity also depends on the proper functioning of *Srotas*, or body channels, which facilitate the movement of nutrients and waste. Blocked channels disrupt immunity, while their purification enhances resilience.
6	Preventive Approach	*Ayurveda* prioritizes prevention through daily and seasonal regimens (*Dinacharya* and *Ritucharya*), dietary guidelines, and lifestyle practices to support long-term immunity and overall health.
7	Adaptogenic Herbs	Many *Ayurvedic* herbs classified as *Rasayana*, such as *Withania somnifera*, *Tinospora cordifolia*, *Cinnamomum zeylanicum*, and *Piper longum*, act as adaptogens, helping the body cope with stress and enhancing immune response.

antioxidant properties further strengthen the immune system by protecting against infections and oxidative damage.

5.3.4 *P. longum L. (Pippali)*

Pippali boosts macrophage activity, regulates cytokine responses for a balanced Th1/Th2 immunity, and enhances the bioavailability of other immune-supporting compounds. Its anti-inflammatory and antimicrobial actions aid in maintaining immune health[10,20].

5.3.5 *Integrated Mechanism of Immunomodulation*

These herbs, individually and synergistically, contribute to immune homeostasis by:

(i) Regulating cytokine networks to balance pro-inflammatory and anti-inflammatory responses.
(ii) Enhancing the innate immune system through macrophage and NK cell activation.
(iii) Strengthening adaptive immunity by promoting T- and B-cell responses.
(iv) Protecting immune cells from oxidative damage via antioxidant mechanisms.
(v) Reducing stress-induced immune suppression through adaptogenic properties[9,21].

5.4 Improvement of Antioxidant Activity

Antioxidants are vital compounds that safeguard cells by neutralising free radicals—unstable molecules formed as byproducts of metabolic processes and through exposure to environmental stressors like pollution, UV radiation, and toxins. Without adequate antioxidant defences, these free radicals can cause oxidative stress, leading to cellular damage and contributing to aging and various chronic diseases. *Ayurvedic* medicine, rooted in natural healing principles, incorporates a wide range of herbs and formulations designed to bolster the body's antioxidant capacity, promoting overall health and resilience against oxidative damage.

In *Ayurveda*, antioxidant activity is primarily attributed to the unique properties (as shown in Table 2) of medicinal herbs and formulations that mitigate oxidative stress and enhance cellular protection. These mechanisms include[10,18,22]:

Ayurveda incorporates a variety of herbs with potent antioxidant properties to combat oxidative stress and promote overall health. These herbs are rich in bioactive compounds that protect cells from free radical damage, reduce inflammation, and enhance the body's natural defence mechanisms. Some key *Ayurvedic* herbs, as shown in Table 3, are known for their antioxidant benefits[10,19], such as:

Table 2. Mechanisms of antioxidant activity in *Ayurveda*

Sl. No.	Antioxidant Activity	Mechanism
1	Free Radical Scavenging:	*Ayurvedic* herbs like *Withania somnifera (Ashwagandha)* and *Tinospora cordifolia (Guduchi)* contain bioactive compounds such as polyphenols, flavonoids, and alkaloids, which neutralize free radicals by donating electrons, thus preventing cellular damage.
2	Enhancing Endogenous Antioxidant Systems:	Several *Ayurvedic* formulations stimulate the production of the body's natural antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which play a crucial role in detoxifying harmful reactive oxygen species (ROS).
3	Metal Chelation:	Herbs like *Cinnamomum zeylanicum* (Cinnamon) and *Piper longum* (Long Pepper) exhibit metal-chelating properties, reducing the catalytic activity of metal ions like iron and copper that accelerate the production of free radicals.
4	Inhibition of Lipid Peroxidation:	*Ayurvedic* botanicals protect cell membranes by preventing the oxidative degradation of lipids, a process that can compromise cellular integrity and function.
5	Modulating Inflammatory Pathways:	Many *Ayurvedic* herbs act on inflammatory mediators, reducing chronic inflammation, which is often associated with increased oxidative stress.
6	Rejuvenation and Tissue Repair:	*Rasayana* therapies in *Ayurveda*, aimed at rejuvenation, enhance tissue repair mechanisms and restore balance in oxidative processes, improving overall resilience.

Table 3. Key *Ayurvedic* herbs with antioxidant properties[10,21,23,24]

Sl. No.	Ayurvedic Herbs	Antioxidant Properties
1	*Withania somnifera (Ashwagandha)*	• Active Compounds: Withanolides, alkaloids, and saponins. • Benefits: Reduces oxidative stress, supports cellular repair, and enhances the body's resistance to environmental and metabolic stressors.
2	*Tinospora cordifolia (Guduchi)*	• Active Compounds: Tinosporine, tinosporaside, and cordifoliosides. • Benefits: Acts as a potent immunomodulator, supports liver detoxification, and neutralizes reactive oxygen species (ROS).
3	*Cinnamomum zeylanicum* (Cinnamon)	• Active Compounds: Piperine and lignans. • Benefits: Prevents lipid peroxidation, scavenges free radicals, and protects against age-related oxidative damage.
4	*Piper longum* (Long Pepper)	• Active Compounds: Vitamin C, tannins, and gallic acid. • Benefits: Enhances bioavailability of other antioxidants, reduces oxidative stress, and protects the cardiovascular system.
5	*Emblica officinalis (Amla)*	• Active Compounds: Curcuminoids and volatile oils. • Benefits: Modulates inflammation, neutralizes free radicals, and enhances the activity of endogenous antioxidant enzymes.
6	*Curcuma longa* (Turmeric)	• Active Compounds: Eugenol, ursolic acid, and rosmarinic acid. • Benefits: Protects against oxidative damage, improves stress adaptation, and supports detoxification.
7	*Ocimum sanctum (Tulsi)*	• Active Compounds: Bacosides and flavonoids. • Benefits: Enhances brain health by reducing oxidative stress in neural cells, supporting memory and cognitive function.
8	*Bacopa monnieri (Brahmi)*	• Active Compounds: Gingerols and shogaols. • Benefits: Reduces inflammation, prevents lipid peroxidation, and enhances antioxidant defences.
9	*Zingiber officinale (Ginger)*	• Active Compounds: Gingerols and shogaols. • Benefits: Reduces inflammation, prevents lipid peroxidation, and enhances antioxidant defences.
10	*Terminalia chebula (Haritaki)*	• Active Compounds: Chebulagic acid, tannins, and flavonoids. • Benefits: Supports detoxification, enhances digestion, and reduces oxidative stress across multiple organ systems.

6. Description and Ethnobotany

6.1 *W. somnifera* (L.) Dunal

Widely recognised as *Ashwagandha*, winter cherry, or Indian ginseng, is a cornerstone of *Ayurvedic* medicine, valued for its extensive therapeutic applications and adaptogenic properties. Known for centuries as a versatile remedy, *Ashwagandha* has been deeply rooted in Indian traditional medicine and is prominently mentioned in the *Vedic* texts as a rejuvenative tonic and functional health supplement. Its status as an official medicinal plant was formalised in 1985 when it was incorporated into the Indian Pharmacopoeia, solidifying its importance in both traditional and modern medical practices. *Ashwagandha* is celebrated as one of the most extensively studied *Rasayana* botanicals in *Ayurveda*, with its roots being particularly prized for their potent medicinal properties. *Ayurvedic* literature highlights its efficacy in addressing conditions across multiple physiological systems, including the nervous, digestive, circulatory, respiratory, reproductive, and urinary systems. Remarkably, *Ashwagandha* is considered safe for use across all life stages, including during pregnancy, with no significant adverse effects reported, underscoring its broad applicability and therapeutic versatility. From a phytochemical

perspective, *Ashwagandha* contains a diverse range of bioactive compounds, including withanolides (notably withaferin A), alkaloids, sitoindosides, and saponins. These compounds contribute to its pharmacological potency, enabling a wide spectrum of biological activities. Modern research, which began intensively in the mid-20th century, has provided robust evidence supporting its therapeutic potential. Studies have demonstrated its immunomodulatory effects, which enhance the body's defence mechanisms, and its antioxidant properties, which protect cells from oxidative damage by neutralising free radicals[1,2]. Beyond its role in boosting immunity, *Ashwagandha* exhibits a multitude of pharmacological actions (Table 4). It has shown significant anti-inflammatory, anticancer, cardioprotective, anti-stress, and antidiabetic properties. Additionally, its neuroprotective effects have made it a promising candidate for managing neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Its antimicrobial and anti-arthritic properties, along with its ability to reduce anxiety and enhance cognitive function, further expand its therapeutic repertoire. *Ashwagandha* is also recognised for its adaptogenic qualities, helping the body maintain homeostasis under stress and improving resilience to physical, emotional, and environmental challenges. Its rejuvenating effects are not limited to specific systems but extend to overall vitality, promoting longevity and enhanced quality of life. In recent decades, the global scientific community has increasingly focused on *Ashwagandha*, integrating its traditional uses with evidence-based approaches to health care. Its applications continue to expand, bridging ancient wisdom with modern science, and establishing *W. somnifera* as a key herb in the realm of integrative medicine[2,10].

6.2 Ethnobotany of *W. somnifera*

The ethnobotanical significance of *W. somnifera*, commonly known as *Ashwagandha*, spans centuries, rooted deeply in the cultural, medicinal, and agricultural traditions of various regions. Its widespread use and cultivation reflect its integral role in traditional medicine systems, particularly *Ayurveda*, as well as in folk remedies across Asia, Africa, and the Mediterranean. *W. somnifera* has been a vital component of *Ayurvedic* medicine for over 3,000 years, with its Sanskrit name "*Ashwagandha*" meaning "smell of a horse," symbolising its perceived ability to impart strength and vitality akin to that of a horse. Ancient texts such as the *Charaka Samhita* and *Sushruta Samhita* describe it as a key *Rasayana* herb, promoting longevity, youthfulness, and overall health. In Unani medicine, it is referred to as '*Asgandh*' and is used to treat inflammation, arthritis, and general debility. Across various cultures, *W. somnifera* is traditionally used to treat ailments such as fatigue, arthritis, anxiety, insomnia, and respiratory disorders. It is also applied to wounds as an anti-inflammatory agent. In rural areas of India and Africa, *Ashwagandha* leaves and roots are sometimes incorporated into food preparations

Table 4. Biological activity of root extracts of *Withania somnifera (Ashwagandha)*[7]

Sl. No.	Root extracts	Biological activity
1	Alcoholic extract	Neurological, Radiosensitizer, Anticonvulsant, Anti-inflammatory, Sedative, Antitumour, Antibacterial.
2	Methanolic extract	GABA mimetic activity GABA receptor mediates anti-convulsant activity, Protective effect as amygdaloid kidlling Anti-inflammatory (70% extract), Anti-stress.
3	Chloroform-Methanol extract	Prevention of Alzheimer's disease, Immunomodulatory, Anti-inflammatory, Nematocidal, Hepatoprotective,
4	Water extract	Nephroprotective, Anti-stress, Antianxiety, Hypothyroidism. Anticonvulsant, Anti-inflammatory, Antiarthritic, Hepatoprotective,
5	Root powder	Antiulcerogenic, Anti-stress, Anticancer and Radiosensitizer, Psychophysiological, Pulmonary tuberculosis, Epilepsy, Nervine tonic, Easy abortion, General tonic in seminal disease, Glandular swellings in bubonic plague, Hypoglycemic-mic diuretic.
6	Decoction	Anticonvulsant, Cold and Chills, Health restorative to old and pregnant.
7	Petroleum ether extract	Insecticidal

for their health-promoting properties. Practitioners have used it as an aphrodisiac and a remedy for male infertility and sexual dysfunction. Indigenous to the Indian subcontinent, *W. somnifera* also grows in parts of the Middle East, Africa, and the Mediterranean region. It thrives in dry, subtropical climates and sandy, well-drained soils. Communities in these regions have cultivated *Ashwagandha* for centuries, not only for medicinal use but also as a protective crop due to its pest-resistant nature. Role in Folk Medicine in African traditional medicine, *W. somnifera* is used for its anti-inflammatory and pain-relieving properties, particularly for rheumatic conditions. In Mediterranean cultures, the plant is employed for wound healing and as a tonic for general health. The traditional applications of *W. somnifera* are well-known all over the world (Table 5). The growing popularity of *Ashwagandha* has raised concerns about overharvesting in the wild, threatening its natural populations in some regions. Efforts are being made to promote sustainable cultivation practices and the conservation of its genetic diversity[25-27].

Ethnobotanical Practices – Harvesting: Traditional practices involve careful harvesting of the roots during the plant's dormancy period for optimal potency. The leaves and berries are also utilised in local remedies. Preparation: The roots are typically dried and powdered for use in decoctions, teas, or capsules. In folk medicine, root paste is applied topically for skin conditions. Trade and Economics: *Ashwagandha* is a valuable cash crop in India, where it is extensively cultivated for domestic use and export. Its demand in the global market has surged due to its recognition in nutraceuticals and alternative medicine.

6.2.1 *T. cordifolia (Willd.) Miers*

Commonly referred to as *Guduchi* in Sanskrit, meaning "the one that protects the entire body",—is a highly esteemed medicinal plant in *Ayurveda*, celebrated for its wide-ranging therapeutic properties. Renowned for its adaptogenic and immunomodulatory effects, *Guduchi* plays a vital role in traditional healing practices and is a cornerstone of several *Ayurvedic* formulations. Widely cultivated across the Indian subcontinent, *T. cordifolia* is deeply integrated into traditional health systems. It is a key ingredient in numerous *Ayurvedic* formulations used to enhance immunity, restore balance in the body, and combat disease conditions. *Guduchi* is traditionally used in the form of decoctions, either as a standalone preparation or in combination with other *Rasayana* herbs like *Terminalia chebula* and *Emblica officinalis*. These synergistic combinations are designed to boost energy, enhance immunity, and promote overall vitality and longevity. *Ayurveda* classifies *T. cordifolia* as a rejuvenating herb, and it has been utilised for centuries to manage a broad spectrum of conditions, including

Table 5. Traditional uses of *Withania somnifera (Ashwagandha)*

Sl. No.	Plant Parts	System of medicine	Uses
1	Leaves	*Ayurveda*	Aphrodisiac, carbuncle, Ulcers, painful swelling[25,28]
		Siddha	Fever, chest pain, sores, swelling[29]
		Unani	External pains, anti-inflammatory[30]
		Folklore	Cure eyesores, boils, diuretic Narcotic, treatment of syphilis and hemorrhoids[26,31]
2	Seeds	*Ayurveda*	Diuretic, narcotic and hypnotic[32]
		Siddha	--
		Unani	--
		Folklore	To coagulate milk, applied on open wounds, Relieving the poison of a serpent rubbed on skin for ringworm in human beings and animals[27,29,32]
3	Roots	*Ayurveda*	Rejuvenating drug, tonic, Alternative pungent, astringent, Aphrodisiac, Phthisis[25,28]
		Siddha	Aphrodisiac, fever, inflammation[29]
		Unani	Asthma, bronchitis, leukoderma, Arthritis, emmenagogue[26,30]
		Folklore	Abortifacient, cold, asthma, Tuberculosis, fever[25,28]
4	Fruits	--	anthelmintic, ulcers and tubercular glands[33]

fever, inflammation, and metabolic disorders. Rich in bioactive compounds such as polysaccharides, lectins, alkaloids, and peptides, *T. cordifolia* demonstrates significant pharmacological potential. Its high content of essential trace elements like zinc and copper contributes to its potent antioxidant activity, which protects cells from oxidative damage. These bioactive constituents have been shown to stimulate the immune system, enhance the production of cytokines, and regulate immune responses, making the plant a powerful immunomodulator[34].

6.2.2 Ethnobotany of T. cordifolia

Tinospora cordifolia, often referred to as *Guduchi* or *Amrita*, occupies a prominent position in the ethnobotanical traditions of South Asia and other tropical regions. Its Sanskrit name, meaning "the one that protects the entire body," underscores its status as a sacred and indispensable plant in *Ayurvedic* medicine. The name of the plant varies largely between regions and languages (Table 6). Found predominantly in India, Sri Lanka, and parts of Southeast Asia, *Guduchi* thrives in tropical and subtropical climates, where it naturally grows as a hardy, climbing shrub. It is typically found entwining itself around trees, often preferring neem *(Azadirachta indica)* as a host, which is believed to enhance its medicinal qualities[35]. Its ability to flourish in a range of conditions—from dense forests to arid plains—makes it a valuable resource for communities across diverse landscapes. The natural behaviour of *T. cordifolia* as a deciduous, perennial plant further adds to its significance. Its extensive root system and adaptive climbing nature make it resilient against environmental stresses, symbolising strength and endurance in traditional cultures. In rural settings, *Guduchi* is often harvested sustainably from the wild or cultivated in home gardens for medicinal and ceremonial purposes. All parts of the plant—the stem, roots, and leaves—are utilised, reflecting its holistic application in traditional medicine. In the cultural context, *Guduchi* is more than a medicinal plant; it holds a revered place in rituals and practices associated with purification and health. *Ayurvedic* texts emphasise its role as a *Rasayana* herb, renowned for its rejuvenating and life-enhancing properties. Traditionally, it has been used to combat ailments ranging from chronic fevers, including malaria and dengue, to inflammatory diseases and metabolic disorders. In combination with other plants such as *Terminalia chebula* and *Emblica officinalis*, *Guduchi* serves as a tonic to promote vitality, boost immune function, and enhance mental clarity. Its role in restoring balance in the body aligns with the *Ayurvedic* principle of *tridosha* harmony, where it is particularly noted for alleviating disorders associated with *Kapha* and *Vata* imbalances[12].

Modern ethnobotanical studies have corroborated the traditional uses of *T. cordifolia*, revealing its rich phytochemical composition. It contains polysaccharides, alkaloids, diterpenoids, and flavonoids, which contribute to its wide-ranging pharmacological properties. Its high concentrations of trace elements like zinc and copper enhance its antioxidant capabilities, protecting cells from oxidative stress and damage. *Guduchi's* immunomodulatory properties, largely attributed to its bioactive compounds, have been shown to stimulate macrophages, T-cells, and cytokine production, supporting the body's defence mechanisms. Additionally, its anti-inflammatory and hepatoprotective effects have been leveraged in managing conditions such as arthritis, liver disorders, and gastrointestinal issues. There are several therapeutic uses for different parts of the plant (Table 7). The geographical distribution and natural adaptability of *T. cordifolia* have ensured its accessibility to diverse populations, reinforcing its importance in both traditional and modern healthcare systems. Its presence

Table 6. Vernacular names of *Tinospora cordifolia* in different regions and languages[36]

Sl. No.	Languages	Names
1	Latin	*Tinospora cordifolia*
2	English	*Gulancha / Indian Tinospora*
3	Sanskrit	*Guduchi, Madhuparni, Chinnaruha, Amrita, Vatsadaani, Tantrika, Kundalini and Chakralakshanika*
4	Hindi	*Giloya, Guduchi*
5	Bengali	*Gulancha*
6	Telegu	*Tippatiga*
7	Tamil	*Shindilakodi*
8	Marethi	*Shindilakodi*
9	Gujarathi	*Galo*
10	Kannada	*Amrita balli*

across the Indian subcontinent and other parts of Asia has made it a cornerstone of indigenous formulations designed to promote health and resilience. Beyond its medicinal value, *Guduchi's* resilience as a plant and its cultural symbolism of immortality and vitality illustrate its profound impact on the communities that rely on it[12].

6.2.3 *C. zeylanicum* Blume (synonym: *C. verum* J. Presl)

Commonly known as *Ceylon Cinnamon*, holds a distinguished place as both a culinary spice and a potent medicinal herb. Derived from the inner bark of the *Cinnamomum* genus, this tropical evergreen tree includes two primary varieties: *C. zeylanicum* (true cinnamon) and *Cinnamomum cassia* (Chinese cinnamon, also known as *Cinnamomum aromaticum*). While both varieties are widely used, *Ceylon Cinnamon* is particularly valued for its milder flavour and enhanced medicinal properties. Beyond its culinary appeal, *Ceylon cinnamon* has a long history of use in traditional medicine. In *Ayurveda*, it is revered for its ability to address respiratory, digestive, and gynaecological disorders. The plant's medicinal versatility extends to its bark, leaves, flowers, fruits, and roots, all of which find applications in both health remedies and flavouring. For instance, cinnamon bark is a key source of volatile oils rich in bioactive compounds like cinnamaldehyde, eugenol, and cinnamic acid. Interestingly, the chemical composition of these oils varies depending on their source—bark, leaves, or roots—resulting in diverse pharmacological effects. One of the key therapeutic attributes of *Ceylon cinnamon* is its anti-inflammatory, antioxidant, and antimicrobial activity. These properties are well-documented, with traditional applications now supported by modern scientific studies. In particular, the antioxidant activity of its phytoconstituents helps combat oxidative stress, while its antimicrobial properties have proven effective against various bacterial and fungal pathogens. Recent research highlights the plant's role as a potent immunomodulator. Active compounds such as cinnamaldehyde and cinnamic acid have been shown to influence both innate and adaptive immune

Table 7. Therapeutic applications of different parts of *Tinospora cordifolia*

Sl. No.	Parts of plant	Therapeutic indications
1	Stem	• Used to treat severe viral infections[37]. • Effective in managing neurological disorders like Parkinson's disease, dementia, and depression. • Acts as an anti-hyperglycemic agent for type-1 and type-2 diabetes. • Alleviates cytokine-induced inflammations. • Boosts immune system function[38]. • Serves as an adjunct therapy during chemotherapy. • Treats digestive issues and improves gut health. • Active against intestinal worms and jaundice when prepared as an infusion from the stem. • Reduces malarial fever through decoction preparations[39,40].
2	Root	• Used to treat HIV infections as a protease inhibitor. • Acts as an alternative to resistant drugs in HIV treatment[39,40]. • Boosts the immune system. • Effective in managing anxiety and depression. • Demonstrates potential in the treatment of colorectal cancer[40]. • Used to reduce and manage inflammation.
3	Bark	• The bark is highly effective in treating unexpected allergic reactions. • Used to alleviate muscle spasms. • Demonstrates efficacy in managing leprosy[37].
4	Leaf	• Highly effective in the treatment of gout. • Leaves are used for managing and healing ulcers[37].
5	Stem + root	• Acts as an antidote against snake bites. • Used to treat skin infections, urinary tract infections, and bronchitis[37].

responses. These effects suggest a promising role for *Ceylon cinnamon* in modulating immune function and addressing inflammatory conditions. Furthermore, its immunotherapeutic potential makes it a candidate for managing autoimmune disorders, infections, and even cancer-related immune dysregulation. The enduring significance of *C. zeylanicum* lies in its multifaceted role, bridging traditional knowledge and contemporary pharmacological advancements. Whether as a flavorful spice or a versatile medicinal agent, *Ceylon cinnamon* remains an integral part of ethnomedicine, with growing evidence to support its therapeutic applications[15,41].

6.2.4 Ethnobotany of C. zeylanicum

Cinnamomum zeylanicum, commonly known as *Ceylon cinnamon*, has a rich history of use that spans thousands of years, both as a culinary spice and a powerful medicinal herb. The term "cinnamon" is generally associated with the dried bark of *Cinnamomum* species, particularly *C. zeylanicum* (true cinnamon) and *Cinnamomum cassia*. It is one of the oldest known spices, highly valued not only for its aromatic flavour but also for its diverse therapeutic properties. Cinnamon's medicinal and culinary applications date back to ancient civilisations. In Egypt, it was used for embalming and mummification due to its preservative and aromatic qualities. In *Ayurvedic* medicine, cinnamon has been employed for centuries as an antiemetic, antidiarrheal, antiflatulent, and stimulant agent, illustrating its wide-ranging therapeutic benefits. Beyond its use in food, cinnamon was also regarded for its healing properties, playing a significant role in traditional healing systems across various cultures. During the 16th and 17th centuries, European trade routes brought *Ceylon cinnamon* from Sri Lanka to European countries, where it gained popularity as a spice and therapeutic agent. The Portuguese and later the Dutch played key roles in the importation and commercialisation of *Ceylon cinnamon*, with the East India Company facilitating its movement into Europe. With time, Sri Lanka became the leading source of cinnamon oils, which are now used in both the pharmaceutical and food industries. Chinese cinnamon oil, derived from *Cinnamomum cassia*, is similarly utilised for its medicinal properties in modern pharmacology[15,41,42].

The genus *Cinnamomum* was formally described in 1760 by Jacob Christian Schaeffer and is distributed across tropical and subtropical regions. The genus comprises approximately 250 species, predominantly found in Southeast Asia, South America, and parts of Australia. These plants thrive in tropical rainforests at varying altitudes, from highland slopes to lowland forests, and are highly sensitive to seasonal climatic changes. *C. zeylanicum* grows as a small evergreen tree that typically reaches heights of 10–15 m. The leaves of the tree are ovate to oblong in shape, measuring 7–18 cm long, and are aromatic when crushed. The flowers are small and greenish, arranged in panicles, while the fruit is a small purple berry containing a single seed. This species thrives in well-drained soils and is most commonly found in Sri Lanka, although it also grows in parts of India and other tropical regions. *C. zeylanicum* and other *Cinnamomum* species have long been used in traditional medicine for a wide range of ailments. The bark, in particular, is valued for its flavour and medicinal qualities, contributing to its widespread use in the preparation of foods, beverages, and medicinal concoctions. *Ceylon cinnamon* is a key ingredient in many traditional remedies, including those for digestive issues, respiratory problems, and gynaecological conditions.

In addition to its culinary uses, cinnamon has a history of applications in various traditional medicines. In Peninsular Malaysia, indigenous groups such as the Sakai ethnic community have used the leaf juice of *Cinnamomum inners* as a poultice for treating rheumatism. Similarly, a decoction of the roots from *Cinnamomum javanicum* has been used to treat fatigue and chest pain, while the bark of *Cinnamomum crassinervium* is applied in paste form to alleviate headaches. Various species, such as *Cinnamomum burmannii* (Java cinnamon), are also used for medicinal purposes, with the bark being a remedy for diarrhoea and malaria. *Cinnamomum* species have strong antimicrobial properties, making them effective in combating fungal, bacterial, and viral infections. In particular, cinnamon is used for its antifungal, antibacterial, and insecticidal activities. Its essential oils are employed in the pharmaceutical and cosmetic industries, where they are used in perfumes, soaps, and mosquito repellents. *Cinnamomum* species are also effective in controlling pests, with applications

in agriculture as larvicidal and nematicidal agents. The parts of the *C. zeylanicum* plant contain a number of biological activities mainly through their extracts or predominant chemical constituents (Table 8). Recent studies have highlighted the pharmacological properties of *Ceylon cinnamon*, confirming its role as an immunomodulator. The active compounds found in the volatile oils of cinnamon, such as cinnamaldehyde, eugenol, and cinnamic acid, are responsible for its antioxidant, anti-inflammatory, and antimicrobial effects. These compounds have been shown to modulate immune responses, enhance antioxidant defences, and reduce inflammation. *Ceylon cinnamon's* immunomodulatory properties make it a promising candidate for further research in the treatment of conditions such as autoimmune diseases, infections, and chronic inflammatory disorders[41,42].

6.2.5 P. longum Linnaeus

Commonly known as long pepper or Indian long pepper, it is a flowering vine belonging to the Piperaceae family. It is a significant medicinal plant in traditional systems like *Ayurveda*, Siddha, and Unani, valued for its therapeutic versatility. Native to the Indo-Malayan region, *P. longum* has been extensively utilised as a spice, condiment, and medicine since ancient times. The plant's bioactive compound, piperine, is responsible for its characteristic pungency and a wide range of pharmacological activities, including immunomodulatory, anti-inflammatory, antioxidant, and bio-enhancing properties. Historically, it was a vital commodity in the spice trade, alongside black pepper and cardamom, contributing significantly to the cultural and economic exchanges between ancient civilizations[44].

Table 8. Biological activity of *Cinnamomum zeylanicum* parts[15,43]

Sl. No.	Parts	Extracts / Chemical constituents	Biological activities
1	Leaf	• Essential oil	• Acaricidal • Ameliorative • Antifungal • Antioxidant and Antimicrobial • Antioxidant
2	Bark	• Unknown • Essential oil • Water extract • Ethanol extract • Essential oil • Chloroform extract • Water extract	• Spermatogenesis • Ovicidal and adulticidal • Antimicrobial • Insecticidal • Cognitive impairment and oxidative stress • Increase sexuality • Anti-asthmatic • Analgesic • Gastroprotective • Insect repellent • Antibacterial and antifungal • Anti-nociceptive and Anti-inflammatory • Antidiabetic • Mutagenic • Antioxidant and antimutagenic

6.2.6 Ethnobotany of P. longum

The use of *P. longum* as a therapeutic agent dates back over 2,000 years, with references in ancient texts like the Charaka Samhita and Sushruta Samhita. In *Ayurveda*, it is categorised as a "*Tridoshic*" herb, capable of balancing the three *doshas—Vata, Pitta*, and *Kapha*. Known as "*Pippali*" in Sanskrit, the name of the plant is different between regions and languages (Table 9). It was traditionally used to treat conditions such as cough, asthma, digestive disorders, and fever. In Traditional Chinese Medicine (TCM), it is known as "*Bi Ba*" and used to improve digestion, alleviate pain, and treat respiratory conditions. The plant was also an important trade commodity during the ancient spice trade, influencing global culinary and medicinal practices. Ethnobotanical surveys across India and Southeast Asia have revealed diverse applications of *P. longum* in folk medicine. Indigenous communities have used their fruits, roots, and leaves for managing colds, tuberculosis, snake bites, and even as an aphrodisiac[32,34]. The plant's versatility and accessibility make it a cornerstone in ethnomedicine, providing insights into its pharmacological promise. *P. longum* is a perennial, dioecious climber that grows up to 1–2 meters in height. The plant features a slender, creeping stem with numerous adventitious roots, which aid in its anchorage and absorption of nutrients. Its leaves are ovate, dark green, alternate, and cordate at the base, measuring approximately 6–9 cm in length. The plant's inflorescence consists of a spike, with male and female flowers on separate plants. Male spikes are longer and slender, while female spikes are shorter and thicker[45,46].

The fruits, which are the primary medicinal and culinary components, are small, ovoid, and borne on short, fleshy spikes. They are initially green and turn red or black upon ripening. The seeds are minute, dark, and embedded within the fruit pulp. The roots, often used in medicine, are slender, aromatic, and slightly bitter. There are several therapeutic uses of *P. longum* as shown in Table 10. *P. longum* is predominantly distributed in tropical and subtropical regions of the Indian subcontinent, Southeast Asia, and the Indonesian archipelago. It is cultivated widely in India, especially in the states of Assam, Meghalaya, Kerala, and Tamil Nadu. The plant also grows in Sri Lanka, Malaysia, Nepal, Bhutan, and parts of Africa. *P. longum* thrives in warm, humid climates, typically in shaded or semi-shaded areas with well-drained soil. It is commonly found in forests, plantations, and agroforestry systems, where it is often intercropped with other spice plants[20,47].

Table 9. Vernacular names of *Piper longum* in different regions and languages[17,45,46]

Sl. No.	Languages	Names
1	Bengali	*Pipul*
2	English	*Long pepper*
3	Gujarati	*Lindi papper*
4	Malayalam	*Pippali*
5	Marathi	*Pippal*
6	Oria	*Pippalimula*
7	Hindi	*Pippal, Pippar*
8	Kannada	*Hippali*
9	Punjabi	*Maghan*
10	Tamil	*Tippili*
11	Telegu	*Pippal chettu*
12	Urdu	*Filfil Daraz*
13	Sanskrit	*Krishnapippali, Magadhi, Pippali, Tikshnatanduli*

7. Phytochemistry

7.1 *W. somnifera* (L.) Dunal

The phytochemical profile of *W. somnifera* has been the subject of extensive research. The chemical characterisation of this plant began in 1911 when Power and Salway isolated an amorphous alkaloid ($C_{12}H_{16}N_2$) from a South African strain of *W. somnifera*. This discovery was later confirmed by Majumdar and Guha in 1933, who identified the same alkaloid in a plant from Bengal, India. In 1955, Majumdar further reported the presence of nicotine and seven other alkaloids in the roots of the plant, naming them (though without detailed structural analysis) as somniferine, somniferinine, somnine, withamine, pseudowithamine, withanmine, and withanaminine. Beyond alkaloids, *W. somnifera* has been found to

Table 10. Common uses of *Piper longum*

Sl. No.	Uses	Details
1	Digestive	*Piper longum* is renowned for its carminative, stomachic, and anthelmintic properties. In traditional medicine, it is used to treat indigestion, flatulence, diarrhea, and colic pain. The plant's alkaloid content stimulates gastric secretions, improving digestion and nutrient absorption[16,48].
2	Respiratory Disorders	The fruits and roots are commonly used to manage cough, asthma, bronchitis, and tuberculosis. *Piper longum* acts as an expectorant, facilitating the expulsion of mucus from the respiratory tract, and its antimicrobial properties aid in treating infections.
3	Fever and Infections	Traditional healers have used *Piper longum* as an antipyretic to manage fever and as an antimicrobial agent to treat bacterial and viral infections. It is also used in formulations for malaria and other febrile illnesses.
4	Reproductive Health	*Piper longum* has been utilized as an aphrodisiac and for addressing infertility issues. The roots are included in formulations for enhancing reproductive health and vitality[16,49].
5	Pain and Inflammation	The plant exhibits analgesic and anti-inflammatory properties, making it a remedy for arthritis, muscle pain, and other inflammatory conditions.
6	Bioavailability Enhancer	The presence of piperine in *Piper longum* enhances the bioavailability of other drugs and nutrients by inhibiting enzymes involved in their metabolism, making it a valuable adjunct in multi-herb formulations[50].

contain a variety of chemical constituents, including steroidal lactones, flavonoids, tannins, saponins, and more. The plant's therapeutic properties are primarily attributed to the bioactive steroidal lactones known as withanolides. These naturally occurring C_{28} steroidal lactones are built on an ergostane framework, either in an intact or rearranged form, where oxidation at C-22 and C-26 results in the formation of a six-membered lactone ring (Figure 9). While withanolides are a defining feature of *W. somnifera*, they are not exclusive to the Solanaceae family. These compounds have also been found in marine organisms like soft corals, as well as in plants from the Taccaceae and Leguminosae families[4,24,51].

To date, over 12 alkaloids, 40 withanolides, and several sitoindosides (which are withanolides that contain a glucose molecule at carbon 27) have been isolated and identified from the aerial parts, roots, and berries of *W. somnifera*. The concentration of the major withanolides typically ranges from 0.001% to 1.5% of the dry weight[4,51,53]. A comprehensive list of the various active compounds isolated from different parts of the plant can be found in Table 11.

Withaferin A (4β, 27-dihydroxyl-1-oxo-5β, 6β-epoxywitha-2-24-dienolide) was the first compound in its class to be isolated from a South Asian strain of *W. somnifera* (Figure 3a), with its structure being elucidated by Lavie *et al.* in 1965. The compound's unique structural characteristics and its notable biological activities triggered an in-depth chemical investigation of the plant, resulting in the identification of several other compounds with similar structural features. Some of the key bioactive molecules derived from this medicinal plant, which show promise for drug development, are presented in Figure 10. Furthermore, research into the roots of *W. somnifera* led to the

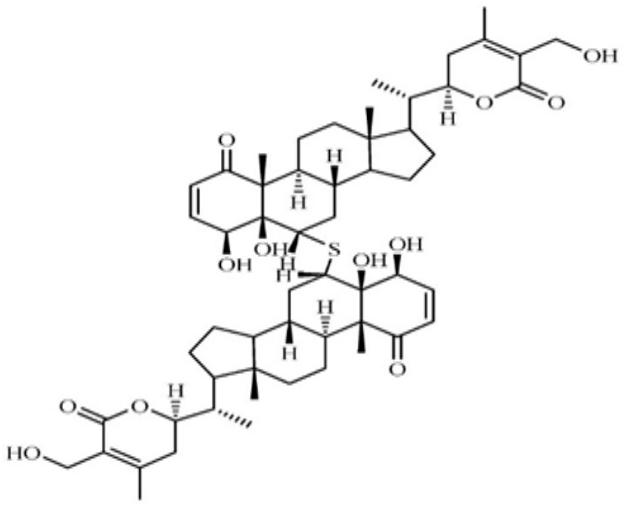


Figure 9. Withanolides - a group of naturally occurring C-28 steroidal lactones built on an intact or rearranged ergostane framework, where C-22 and C-26 are oxidised, forming a six-membered lactone ring[52].

Table 11. The different active compounds isolated from various parts of *Withania somnifera*

Sl. No.	Plants Parts	Chemical Constituent
1	Roots	Sitoindosides VII (Acylsteryl-glucoside)54
		Sitoindosides VIII (Acylsteryl-glucoside)54
		Sitoindosides IX (Glycowithanolide)55
		Sitoindosides X (Glycowithanolide)55
		Withanine (Alkaloid)56
		Withananine (Alkaloid)56
		Ashwagandhanolide57,58
2	Leaves	Withaferin (Steroidal lactone)59
		Withaferin A (Steroidal lactone)60-62
		Withanolie D (Steroidal lactone)59,60
		Withanolie E (Steroidal lactone)63
		Withanone (Steroidal lactone)60,65
		Withanolide Z (Novel)56
		Withanolide B56
		7-hydroxywithanolide56
		3α-methoxy-2, 3-dihydro-66
		27-deoxywithaferin A (Steroidal lactone)60
		4β, 17α-dihydroxy-1-1oxo-61
		5β, 6β-epoxy-22R-witha-62
		2, 24-dienolide (steroidal lactone)60,62
		4β-dihydroxy-5β, 6β-epoxy-64
		1-oxo-22R-witha-2, 14-24-65
		Trienolide (steroidal lactone)60
		5, 20α (R)-dihydroxy-6α, 7α-epoxy-1-oxo- (5α) - Witha-2, 24-dienolide (steroidal lactone) 2, 3-dihydrowithaferin A-3beta-O-sulfate65
3	Seeds	Withanolide –WS 2 (aliphatic ester)67
		Withanolide –WS 1 (aliphatic ketone)68

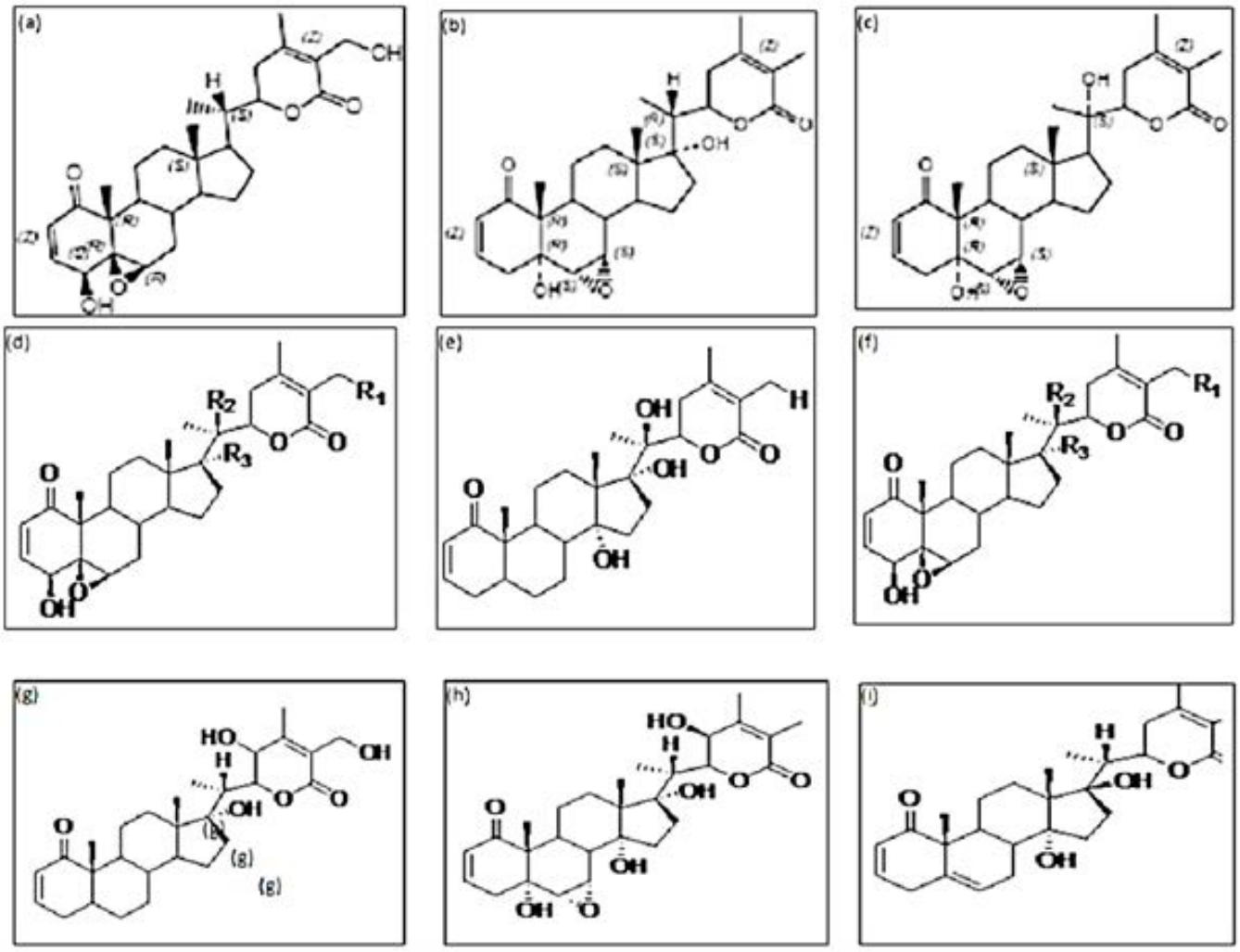


Figure 10. Some bioactive molecules and their chemical structures isolated from *W. somnifera*[4,7,10]. (A) Withaferin A, (B) Withanone, (C) Withanolide A, (D) Withanolide D,(E) Withanolide E, (F) Withanolide G, (G) Withanolide Q, (H) Withanolide R, (I) Withanolide P.

discovery of a novel dimeric thiowithanolide, named *Ashwagandha*nolide[7,22,51], as depicted in Figure 11. The phytochemistry of *W. somnifera* has been discussed in Table 12.

7.2 *T. cordifolia* (Willd.) Miers

Phytochemical analysis of *T. cordifolia* has revealed a diverse range of over 200 different compounds from various chemical classes, with diterpenoids being the most abundant. Notably, *T. cordifolia* contains specific diterpenoids, such as cordifolides, which have a clerodane-type skeleton. These can be categorised into two types: Type 1, which includes a C-8/C-12 linking lactone ring, and Type 2, which lacks this feature. However, *T. cordifolia* does not share certain

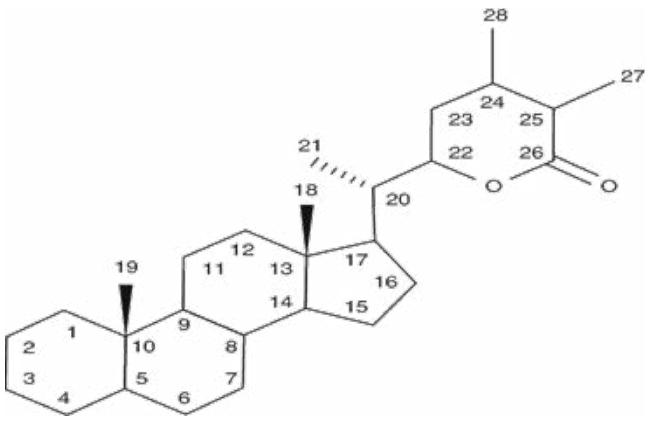


Figure 11. *Ashwagandha* nolide: a unique thio-dimer of withanolide isolated from the roots of *W. somnifera*[7,10].

diterpenes found in other species of *Tinospora*, such as *T. rumphii*, *T. crispa*, and *T. baenzigeri*. In addition to the diterpenoids, *T. cordifolia* is distinguished by the presence of unique compounds like tinosponone and tinocordioside, which are tricyclic terpenes containing a cyclobutene ring. The plant also features daucane-type sesquiterpenes, such as tinocordifolioside, tinocordifolioside acetate, and tinocordifilin, as well as the monoterpenoid angelicoidenol-2-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside. Alkaloids are another significant class of compounds in *T. cordifolia*, including berberine-class alkaloids like palmatine, reticuline, and jatrorrhizine, as well as aporphine-class alkaloids such as magnoflorine, menisperine, tinoscoroside A, and tinoscoroside B. Other important chemical classes found in *T. cordifolia* include steroids (notably β-sitosterol derivatives) and polysaccharides like glucose, arabinose, xylose, galactose, rhamnose, and mannose[63,69,70]. A more detailed list of these phytochemicals and their specific plant sources is available in Table 13.

Table 12. Phytochemistry of *Withania somnifera*[4,23,53]

Sl. No.	Class	Chemical constituents	Activity	Plant part
1	Alkaloids	Ashwagandhine, cuscohygrine, anahygrine, tropine	antispasmodic effects, anti-microbial activity sedative effects.	Root
2	Steroidal activity	Ergostane, steroidal lactones, withaferin A, withasomniferin- A.	The antioxidant as well as Aphrodisiac reduces cholesterol levels, affects the immune system and tumor cells.	Root
3	Saponins	Sitoindoside IX and X Sitoindosides - VII and VIII	Antioxidant, Adaptogenic.	Root
4	Aqueous extract	Withanolides, Glycowithanolides	Immunomodulatory.	Root
5	Bioactive compounds	Withanolide sulfoxide	Antimicrobial activity carcinogens tumor promoters, and inflammatory agents.	Root, Leaf
6	Ethanolic	Ethanol	anti-proliferative activity against cancer cell, Antibacterial.	leaf, stem and root
7	Root Extract	–	Anti-Parkinson's, cardioprotective, neuroprotective.	Root

Table 13. Phytochemistry and pharmacology of *Tinospora cordifolia*

Sl. No.	Phytoactive Constituent	Class	Plant Part	Activity
1	Cordifolioside	Phenylpropanoid Glycoside	Stem	↑ phagocytosis[61,66,71]
2	Syringin	Phenylpropanoid Glycoside	Stem	↑ phagocytosis[36,66]
3	Cordioside	Clerodane furano diterpene	Stem	↑ phagocytosis[38]
4	Magnoflorine	Benzylisoquinoline alkaloid	Stem, Root	↑ phagocytosis; ↑ ROS[66]
5	N-Formylannonain	Benzylisoquinoline alkaloid	Stem, Root	↑ phagocytosis; ↑ ROS[66]
6	Tinocordiside	Cadinane sesquiterpene	Stem	↑ phagocytosis; ↑ ROS[66]
7	11-hydroxymuskatone	Cadinane sesquiterpene	Stem	↑ phagocytosis; ↑ ROS[72]
8	G1-4A	Arabinogalactan polysaccharide	Stem	↑ Mortality (LPS septicaemia model)[73]; ↑ Th1, ↑ Th2 cytokines[74]; "macrophage activation; ↑ mitogenesis[75]
9	RR1	a-D-glucan polysaccharide	Aerial Parts	↑ phagocytosis; ↑ Th1 cytokines[76]
10	Guduchi Immunomodulatory protein (ImP)	Protein	Stem	↑ phagocytosis; ↑ mitogenesis; ↑ bactericidal[77]

7.3 *C. zeylanicum* Blume (synonym: *C. verum* J.Presl)

Cinnamomum zeylanicum comprises two key chemical groups: polyphenols and volatile phenols. Among its polyphenolic constituents are ferulic acid, caffeic acid, gallic acid, vanillic acid, protocatechuic acid, and p-coumaric acid, alongside other notable polyphenols (Figure 12a). These compounds are central to the plant's antioxidant properties and therapeutic potential. The composition of essential oils from *C. zeylanicum* varies based on the specific plant part used for extraction. Bark oil is particularly rich in cinnamaldehyde, which constitutes 62% to 90% of the oil and is largely responsible for the characteristic scent and various pharmacological activities associated with cinnamon. Additionally, bark oil contains other minor volatile compounds, such as hydrocarbons and oxygenated substances like benzyl benzoate, β-caryophyllene, cinnamyl acetate, linalool, and eugenyl acetate (Figure 12b). Eugenol is the primary constituent of leaf oil, with concentrations typically exceeding 80%[78]. This compound is also prevalent in oils extracted from cinnamon flowers and fruits. Other significant volatile components in these parts include (E)-cinnamyl acetate and β-caryophyllene (Figure 12b). The distinct chemical profiles of different plant parts and the present bioactive compounds (Table 14) highlight the versatility of *C. zeylanicum* for diverse applications in medicine, perfumery, and cuisine[77,79].

7.4 *P. longum* Linnaeus

Piper longum, commonly known as long pepper, is a rich reservoir of bioactive compounds with diverse pharmacological and therapeutic properties. Its phytochemical profile spans various classes of secondary metabolites, including alkaloids, lignans, essential oils, and fatty acids, which contribute to its wide-ranging biological activities (Table 15)[17,45].

The fruits and seeds of *P. longum* also contain compounds such as β-sitosterol, dihydrostigmasterol, dieudesmin, n-hexadecane, n-heptadecane, n-octadecane, and n-nonadecane. In addition, unsaturated amides such as n-isobutyl-deca-trans-4-dieneamide have been reported[50].

8. Immunomodulation

8.1 Immunomodulation of *W. somnifera* (L.) Dunal

Withania somnifera, commonly known as *Ashwagandha*, is recognised as a potent immune stimulator, exhibiting significant therapeutic potential across a range of diseases (Figure 13). Its pharmacological effects include anti-tumour, anti-stress, anti-inflammatory, and immunomodulatory activities, contributing to a more balanced and beneficial immune response. Notably, *W. somnifera* has shown promise in modulating conditions characterised by exaggerated immune responses, such as robust Th2-mediated inflammation and airway hyperresponsiveness (Figures 14 and 15). There are

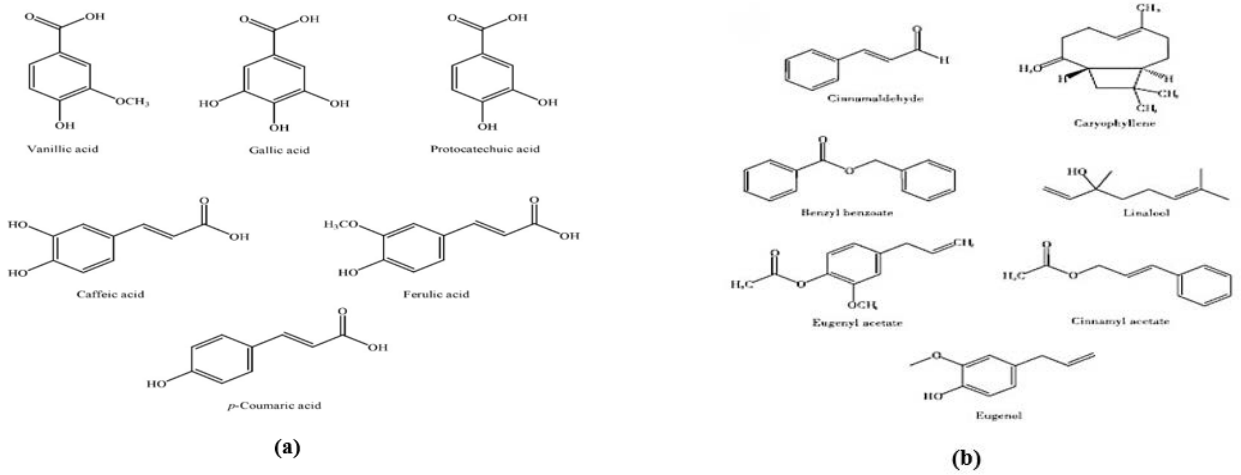


Figure 12 (a). Polyphenolic constituents; (b). Chemical compounds of cinnamon essential oil[43,80].

Table 14. Bioactive compounds from *Cinnamomum zeylanicum*

Sl. No.	Bioactive compounds	Details
1	**Eugenol**	Eugenol ($C_{10}H_{12}O_2$), a well-known volatile compound predominantly associated with clove extracts, is also a key constituent of cinnamon, particularly concentrated in the leaves. Research by Rao et al. highlighted that eugenol levels are significantly higher in the larger, upper leaves of the cinnamon plant, underscoring its variability within plant morphology. In cinnamon bark, eugenol content in essential oil ranges from 4.6% to 7.45%, while in the leaves, it constitutes up to 58.10% of the essential oil and 10.97% of the methanolic bark extract. Despite its notable antioxidant properties, eugenol's potential cytotoxicity at elevated doses necessitates further investigation to establish its pharmacological safety profile. Interestingly, eugenol is absent in cinnamon's ethanolic extract, indicating selective solubility and variation in extraction methods. These findings suggest that eugenol-rich fractions of cinnamon could serve as a valuable resource in medicinal and therapeutic applications, albeit with careful consideration of dosage and formulation15,79.
2	**Cinnamaldehyde**	Cinnamaldehyde (C_9H_8O), a volatile aldehyde derivative, is the compound primarily responsible for the distinct flavor and aroma of cinnamon. This natural flavonoid constitutes approximately 90% of the essential oil extracted from cinnamon bark. Studies by Kallel and Behbahani et al. confirm cinnamaldehyde as the dominant bioactive constituent in Cinnamomum zeylanicum essential oil, making up about 71.5% to 77.34% of its composition. Additionally, Seroyi et al. reported cinnamaldehyde concentrations as high as 82.6% in water extracts, though its presence in methanol and ethanol extracts is notably lower, measured at 14.63 ± 1.1 mg/g and 38.78 ± 0.78 mg/g, respectively. The compound has been extensively studied for its therapeutic potential, particularly as an antidiabetic agent. Research by Babu et al. demonstrated that cinnamaldehyde, in combination with glibenclamide, effectively reduces hyperglycemia in diabetic rats. It was shown to lower total cholesterol and triglyceride levels while increasing high-density lipoprotein (HDL). Moreover, cinnamaldehyde enhances the activity of glucose transporter 4 (GLUT 4), thereby facilitating cellular glucose uptake and reducing blood glucose levels. Beyond its antidiabetic properties, cinnamaldehyde exhibits potent antioxidant activity, making it a compound of significant interest for pharmacological and therapeutic applications43,81.
3	**Cinnamic Acid**	Cinnamic acid ($C_9H_8O_2$), a compound derived through the deamination of phenylalanine, is a key constituent of cinnamon bark. It is characterized by low toxicity and a wide range of biological activities, particularly its antimicrobial properties. Found in varying concentrations across different extracts of cinnamon, cinnamic acid is present at 1.0 mg/g in water extracts, 0.68 ± 0.01 mg/g in methanolic extracts, and 8.99 ± 0.5 mg/g in ethanolic extracts. The compound's phenolic hydroxyl groups contribute significantly to its antioxidant activity. Furthermore, cinnamic acid has demonstrated notable antibacterial, antiviral, and antifungal properties, making it a valuable compound in pharmacological and therapeutic applications. Its multifunctional bioactivity highlights its importance in both traditional medicine and modern drug development.
4	**Linalool**	Linalool ($C_{10}H_{18}O$), a prominent bioactive compound, is a key component of cinnamon essential oil, particularly in its leaves. The concentration of linalool in cinnamon leaf essential oil is notably high, reaching approximately 85.7%, while it constitutes about 7% of the essential oil derived from the bark. This compound significantly contributes to the characteristic flavor and aroma of cinnamon, with higher linalool content enhancing the sensory appeal and potential therapeutic applications of the essential oil.
5	**β-Caryophyllene**	β-Caryophyllene ($C_{15}H_{24}$), a sesquiterpene widely recognized in clove essential oil, is also a notable component of cinnamon, with concentrations ranging from 2.8% to 6.4%. This compound exhibits a range of therapeutic properties, including anti-inflammatory, antibiotic, antioxidant, and anti-carcinogenic activities. Its presence in cinnamon contributes to the plant's medicinal value, enhancing its potential in various pharmacological applications.

Table 14. Continued…

6	**Coumarin**	Coumarin, a naturally occurring phytochemical, is present in both aqueous and methanolic extracts of cinnamon. In the methanolic extract, its concentration is measured at 4.4 ± 0.10 mg/g, while the water extract contains approximately 4.8 mg/g. Known for its fragrant aroma and bioactive properties, coumarin plays a significant role in the therapeutic potential of cinnamon, contributing to its pharmacological profile14,81.
7	**Trans-Cinnamyl Acetate**	Trans-cinnamyl acetate ($C_{11}H_{12}O_2$), an ester derived from the condensation of cinnamyl alcohol and acetic acid, is a notable constituent of cinnamon leaf oil. It is present at concentrations of 23.7% in the leaves and 4.98% in the bark essential oil. This compound is valued for its versatile applications, serving as a fragrance component, a biological metabolite, and an insecticidal agent, highlighting its significance in both aromatic and functional uses.
8	**1,8-Cineole**	1,8-Cineole ($C_{10}H_{18}O$), commonly referred to as eucalyptol, is a naturally occurring monoterpenoid found in the essential oils of numerous aromatic plants, including cinnamon. In cinnamon, the concentration of 1,8-cineole differs depending on the plant part: it constitutes 6.39% of the root oil, 3.19% to 5.4% of the bark oil, and 3.4% of the water extract. This compound is known for its aromatic properties and potential therapeutic applications, adding to the medicinal value of cinnamon42,44.

Table 15. Various classes of secondary metabolites in *Piper longum*

Sl. No.	Secondary metabolites	Details
1	**Alkaloids**	Alkaloids form a significant portion of the bioactive compounds in *Piper longum*. The fruit contains alkaloids such as piperine (4–5% in spikes), piperlongumine, piperlonguminine, and piplartine. Other alkaloids isolated include piplatin, pipernonaline, and new alkaloids like piperolactam A, piperolactam B, and piporadione. The roots of the plant also contain piperlongumine (0.02%) and piperlonguminine (0.2–0.25%). Further investigation into *Piper longum* has yielded unique alkaloids such as cepharadione A, cepharadione B, cepharanone B, aristolactam A, and aristolactam AII. These compounds are closely related to pellitorine. Several dioxoaporphines, including nor-cepharadione B and 2-hydroxy-1-methoxy-6-methyl-4H-dibenzoquinoline-4,5-dione, have also been identified[20,46].
2	**Essential Oils**	Steam distillation of dried spikes yields 0.7% essential oil with a characteristic spicy aroma resembling pepper and ginger. The essential oil contains long-chain hydrocarbons, monoterpenes, and sesquiterpenes, with caryophyllene as the dominant compound. Other components include zingiberene, α-thujene, p-cymene, terpinolene, dehydrocarveol, and β-methoxyacetophenone.
3	**Lignans**	Lignans isolated from *Piper longum* include sesamine, pluristilol, fargosin, asarinine, guineensine, and pipereide. These lignans contribute to the plant's antioxidant and pharmacological properties[16,48].
4	**Fatty Acids**	The plant contains a variety of fatty acids, including **palmitic, hexadecenoic, stearic, oleic, linoleic, linolenic, arachidic,** and **behenic acids**. These compounds add to the plant's nutritional and medicinal value.
5	**Amino Acids**	Free amino acids such as L-tyrosine, **L-cysteine hydrochloride, DL-serine**, and **L-aspartic acid** have been detected in the fruits of *Piper longum*. These amino acids may play a role in its therapeutic applications[49,83].

several immunomodulatory effects of *W. somnifera* in various diseases (Table 16).

Role in Balancing Immune Responses – *W. somnifera* has demonstrated the ability to regulate Th1 and Th2 immune responses, which are crucial for maintaining immune equilibrium. Preclinical studies on mice revealed that *W. somnifera* enhances Th1-mediated immunity by increasing CD4+ and CD8+ T cells, thus balancing the Th2-Th1 axis. This modulation is particularly relevant in allergic and hyperactive immune conditions. For instance, in murine models of asthma, pre-treatment with withaferin A, an active compound isolated from *W. somnifera*, at doses of 20–80 mg/kg significantly reduced airway inflammation.

Table 16. Immunomodulatory effects of *Withania somnifera* in various diseases

Sl. No.	Form of W.S.	Immunomodulatory effects of WS	Involved diseases
1	*Withania somnifera* root, leaf extract	Increase levels of immunoglobulins, IFN-gamma, CD3+ and CD4+ T-cells, T-helper 1 (Th1) cytokines and CD8+ T-cells[84]	Viral diseases
2	*Withania somnifera* root powder	Increased Natural cells (NK) cells activity[56,84]	Ovarian cancer
3	Withaferin A	Inhibition of NF-kB activity and pro-inflammatory and stress response mediators (TNFα, COX-2, and iNOS)[85,86]	Inflammatory diseases
4	Withaferin A	Inhibits neutrophil adhesion, migration, and respiratory burst[86,87]	Acute lung injury, acute pancreatitis, gout and apoptosis
5	*Withania somnifera* root and leaf extracts	Maintain the normal levels for urine sugar, blood glucose, haemoglobin (Hb), glycosylated haemoglobin (HbA1C), liver glycogen, serum and tissues lipids, serum and tissues proteins, liver glucose-6-phosphatase (G6P) and serum enzymes like aspartate transaminase (AST), alanine transaminase (ALT), acid phosphatase (ACP) and alkaline phosphatase (ALP)[88]	Hypoglycaemic and hypolipidaemic activities in Diabetes mellitus (DM)
6	*Withania somnifera* root	Reduce serum urea, creatinine89	kidney dysfunction
7	Aqueous root extract of *Withania somnifera*	Significantly reduce the elevated hepatotoxicity biomarkers, decrease lipid peroxidation, and enhance glutathione, catalase, glutathione reductase, and glutathione peroxidase activity[90]	Liver injury, systematic inflammation, and liver cancer
8	Ethanolic extract of *Withania somnifera*	Protected against γ radiation-induced hepatotoxicity, decreased serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase; decreased hepatic levels of malondialdehyde and total nitrate/nitrite; and increased hepatic antioxidant enzymes, including superoxide dismutase and glutathione peroxidase[91]	Liver injury
9	Aqueous extract of *Withania somnifera* roots	Attenuate pro inflammatory cytokines including TNF-α, IL-1β, IL-6, transcription factor NF-κB and increasing anti-inflammatory cytokine IL-1092	Arthritis

This was achieved by downregulating the expression of pro-inflammatory cytokines in the lungs, leading to a reduction in airway hyperresponsiveness. These findings suggest that *W. somnifera* functions as a natural immunomodulator, comparable to synthetic adjuvants, in mitigating pathological immune responses while maintaining overall immune health[4,23,24].

8.2 Mechanism of Action and Immune Receptor Activation

The immunomodulatory effects of *W. somnifera* are believed to arise from its interaction with immune receptors such as Toll-like receptor 3 (TLR3) and Toll-like receptor 9 (TLR9) on innate immune cells like dendritic cells. Activation of these receptors initiates downstream signalling pathways that enhance adaptive immunity. Adjuvants, substances used to enhance immune responses, generally fall into two categories based on their impact on Th1 (cell-mediated) or Th2 (humoral) immunity. Th1-promoting adjuvants, such as double-stranded RNA (dsRNA), activate innate immune sensors like TLR3. This activation stimulates the expression of interferon-stimulated genes (ISGs) and the recruitment of immune cells essential for viral clearance and pathogen elimination. By promoting Th1 responses, these adjuvants also suppress Th2-mediated responses, which are often hyperactive in allergic and inflammatory conditions.

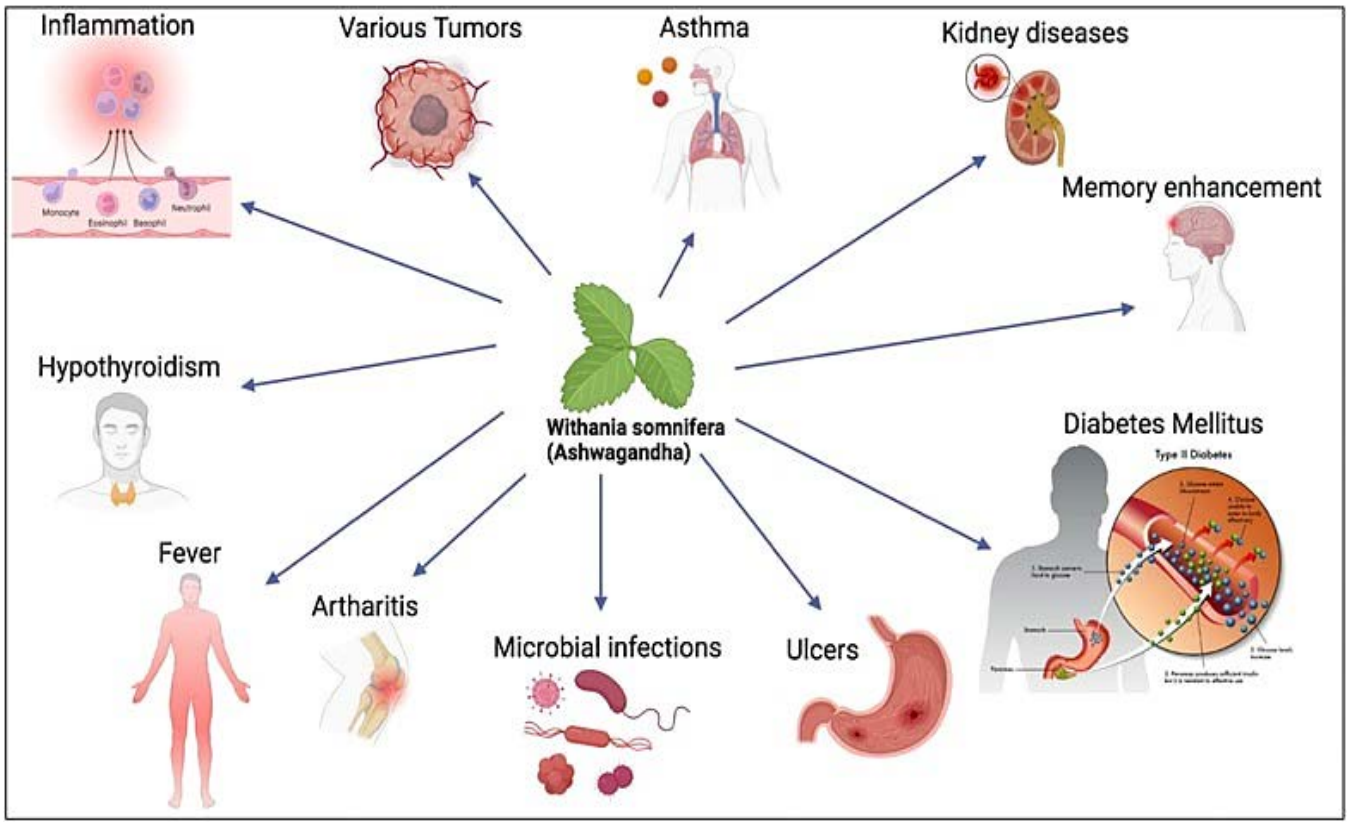


Figure 13. *Withania somnifera* is widely utilized as a botanical remedy for managing various chronic conditions, including asthma, kidney disorders, diabetes mellitus, and more[7,10].

Withania somnifera has emerged as a candidate adjuvant due to its ability to mimic these effects, reducing Th2-driven pathologies while bolstering Th1-mediated protective immunity. Its potential applications in preventing and treating hyperimmune or immune-deficient states warrant further exploration in clinical settings[10,24,51].

8.3 Immunomodulation of *T. cordifolia* (Willd.) Miers

Tinospora cordifolia, commonly known as *Guduchi*, is widely recognised for its robust immunomodulatory effects. This plant primarily stimulates non-specific immune mechanisms through bioactive components, including polysaccharides and alkaloids[34].

Key Immunomodulatory Constituents – The active fraction responsible for the plant's immunomodulatory effects is a polysaccharide comprising glucose, fructose, and arabinose as monomeric units. Additional bioactive compounds include 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside, and syringin.

8.3.1 Polysaccharides and Proteins

An immunomodulatory protein (ImP) isolated from the stem, absent in leaves, is a single-chain acidic protein (~25 kDa) devoid of glycan groups. It promotes lymphocyte proliferation and macrophage activation, enhancing innate immune responses.

Another prominent component, G1-4A, functions as a non-microbial TLR4 agonist found on macrophages and B lymphocytes. Stimulation with G1-4A induces macrophage activation, B cell proliferation, and increased cellularity in immune organs such as the spleen[93].

8.3.2 Macrophage Activation and Cytokine Modulation

Tinospora cordifolia treatment enhances the activity of enzymes such as NADH-oxidase, NADPH-oxidase, and myeloperoxidase, which are critical for

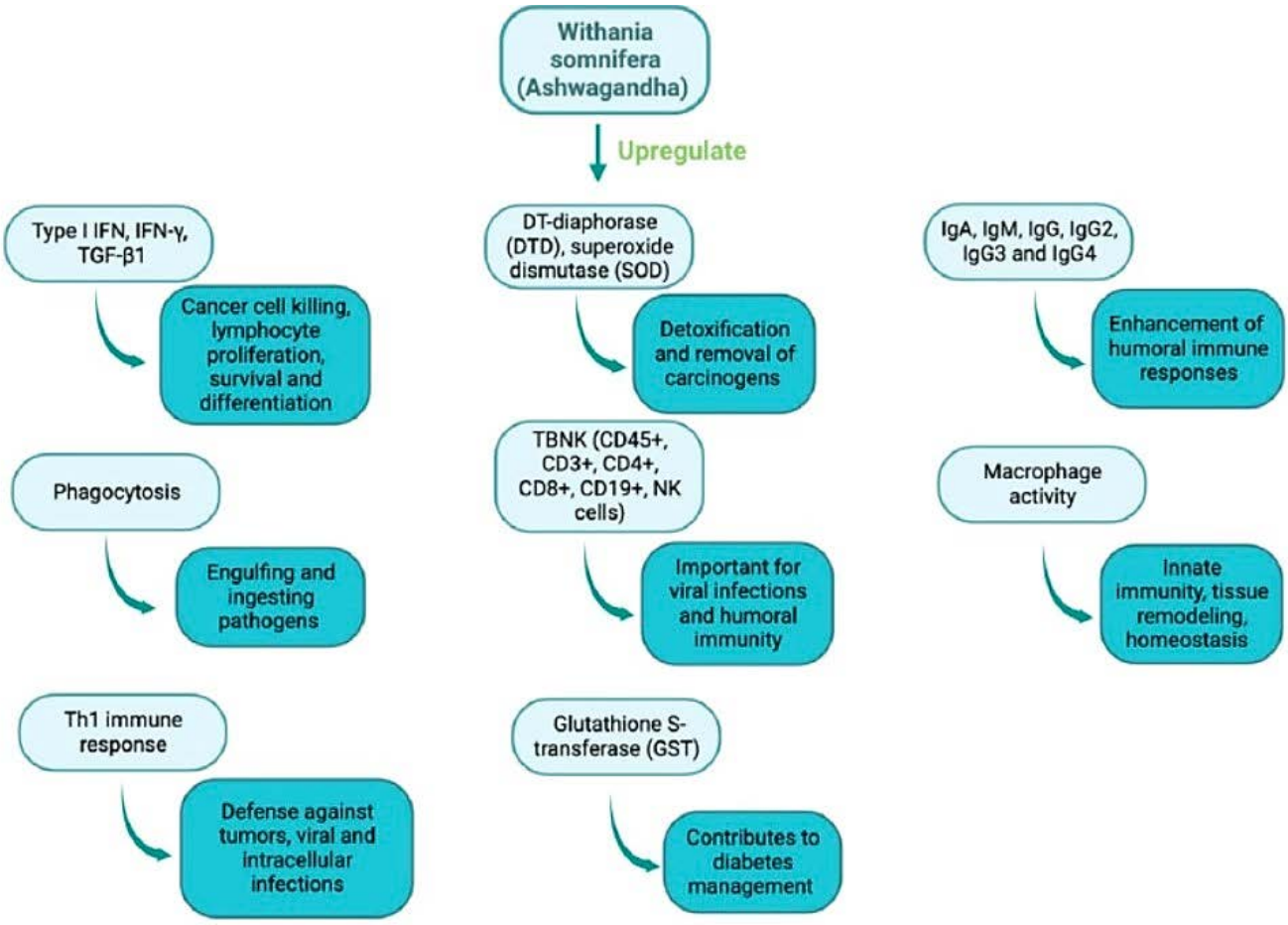


Figure 14. The immunomodulatory effects of *Withania somnifera* are achieved by upregulating immune mediators, enhancing cytokine production, activating immune cells, and boosting the activity of immune-related enzymes[2,4].

macrophage activation. It also promotes phagocytic activity and nitric oxide (NO) production, restoring immune functions diminished by toxins like carbon tetrachloride (CCl4).

8.3.3 Anti-Inflammatory and Immunostimulatory Effects

Guduchi extract shifts immune responses from Th2 to Th1 when combined with cisplatin in treating visceral leishmaniasis in murine models, reducing cisplatin's adverse effects.

Local infusion of hydro-methanolic extract into the mammary gland enhances immunity against mastitis-causing bacteria by increasing IL-8 levels, phagocytic activity, and lysosomal enzyme content in milk polymorphonuclear cells[13,63]. Some applications towards immunotherapy of *T. cordifolia* are mentioned in Table 17.

Guduchi treatment has demonstrated notable antibacterial effects, including enhanced macrophage phagocytosis against both infective (*e.g.*, *Escherichia coli*) and non-infective (*e.g.*, heat-killed yeast) microorganisms. It also supports cell survival by upregulating anti-apoptotic gene expression, further consolidating its role in immune resilience[12].

The diverse immunomodulatory mechanisms of *T. cordifolia* underscore its immense therapeutic potential (Figure 16). By restoring macrophage function, enhancing lymphocyte activity, and modulating cytokine responses, *guduchi* serves as a versatile immunotherapeutic agent (Table 18). Further exploration of its molecular pathways and clinical applications will help maximise its benefits in managing

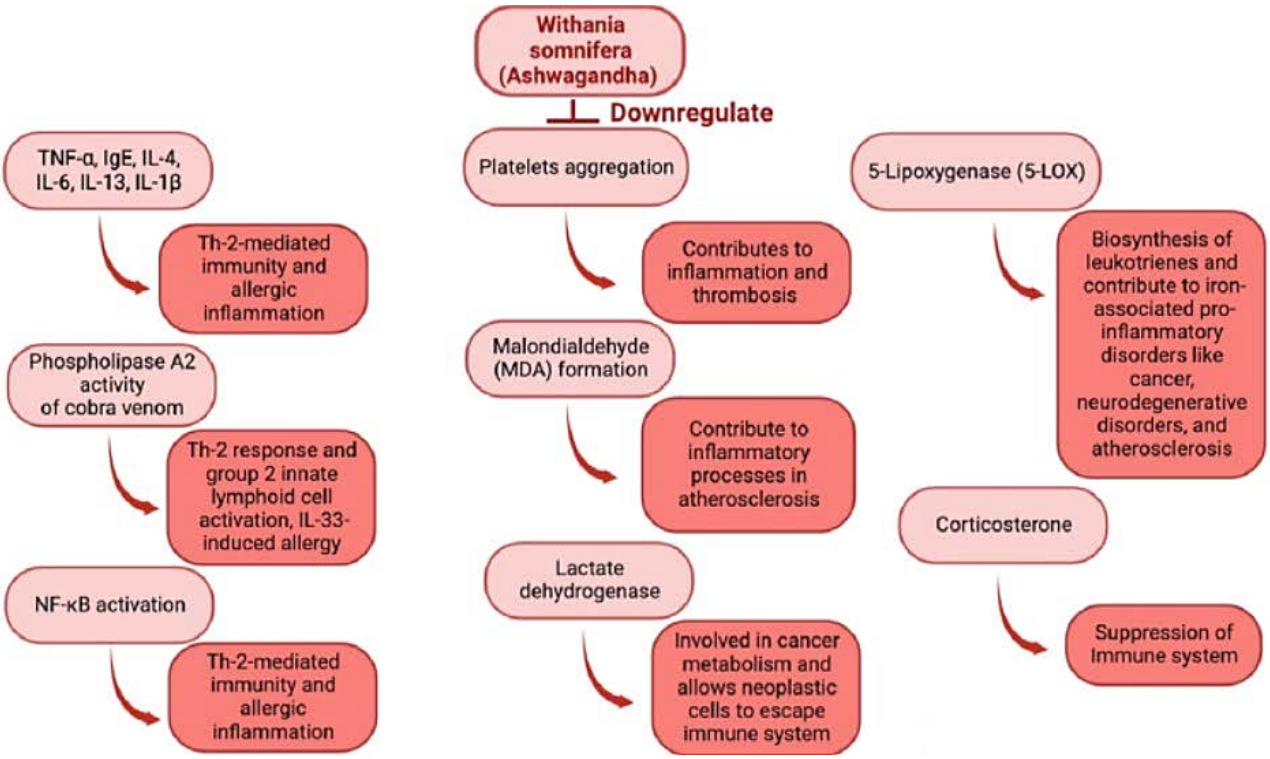


Figure 15. The immunomodulatory effects of *Withania somnifera* also involve downregulating specific immune mediators, cytokines, cells, and enzymes to control excessive immune responses and maintain immune homeostasis[1,2].

Table 17. Applications in Immunotherapy[12,36]

Sl. No.	Applications	Details
1	**Adjunct to Anti-retroviral Therapy (ART):**	*Guduchi*, when incorporated into ART for HIV, enhances treatment outcomes by improving immune responses and addressing drug resistance.
2	**Pediatric Immune Boosting:**	In infants, *Tinospora cordifolia* is a key component of the "Bala compound," traditionally used to enhance immunoglobulin synthesis and fortify immunity.
3	**Herbal Compositions and Patents:**	o LIVZON: A patented *Ayurvedic* composition by Rohatgi, designed for prophylaxis and treatment of hepatitis, liver sclerosis, AIDS, flu, and TB by boosting both cellular and humoral immunity. o Anti-Allergic Combinations: A herbal formulation patented by the Pushpangadan group, containing guduchi, reduces histamine levels and alleviates allergic responses.

immune-related disorders[94]. Several compounds of *T. cordifolia*, which have immunomodulatory activities, are mentioned in Table 19.

8.3.4 Immunomodulation of C. zeylanicum Blume (synonym: C. verum J.Presl)

Cinnamomum zeylanicum, commonly known as *Ceylon cinnamon*, is recognised not only for its rich aroma and flavour but also for its significant antioxidant and immunomodulatory properties (Table 20). Antioxidants play a pivotal role in maintaining cellular integrity by neutralising Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which are byproducts of cellular metabolism. The mechanism of *C. zeylanicum* antioxidant activity is discussed in Table 21. When present in excess, these molecules can cause oxidative stress, which leads to cellular damage, including DNA mutations, protein modifications, and lipid peroxidation. Such oxidative damage is particularly detrimental to the immune system, as it

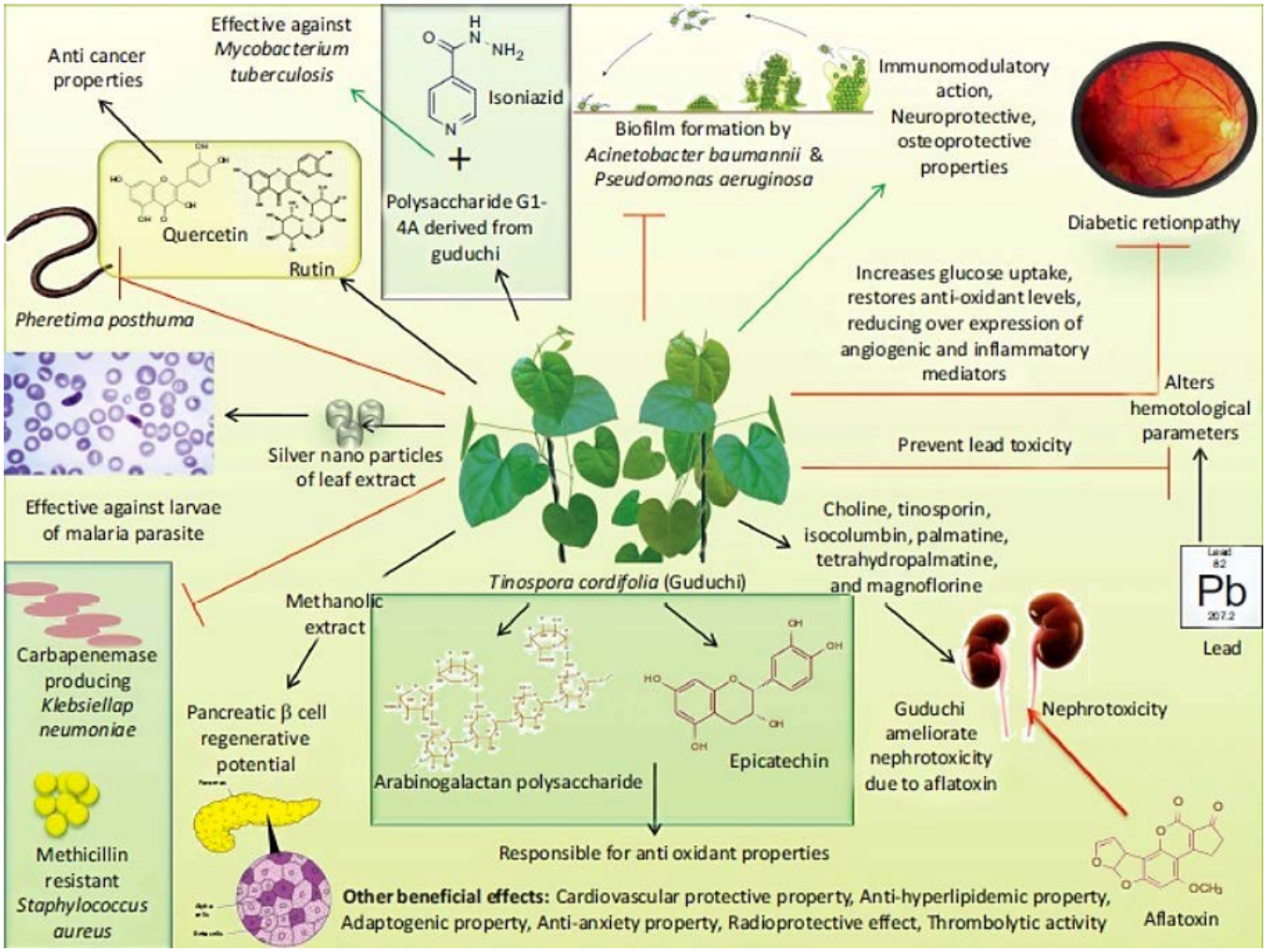


Figure 16. An overview on medicinal and beneficial health applications of *Tinospora cordifolia*[69,93].

Table 18. Compounds of *Tinospora cordifolia* which have immunomodulatory activities[12]

Sl. No.	Compounds	Immunomodulatory activities
1	Cordifolioside A	immune system stimulating properties
2	Hydroxymustakone, N-methyl-2 pyrrolidone	nitric oxide production enhancing properties
3	Magnoflorine, tinocordiside, N-formylannonain	phagocytic activity enhancing properties
4	G1-4A, Guduchi imp protein	Potential immunomodulator.
5	Cordioside	An immunomodulator
6	Cordifolioside B	Stimulatory effects on immune system
7	Ecdysteron	immune system stimulating properties
8	Syringin	Potential immunomodulator

can either impair immune cell function or provoke inflammation, thus contributing to the development of various diseases, including cancer, autoimmune disorders, and cardiovascular conditions[14,78,95]. Phytochemical Constituents that are responsible for antioxidant activity in *C. zeylanicum* are explained in Table 22.

By modulating oxidative stress, *C. zeylanicum* plays a key role in supporting the immune system. Research has demonstrated that its antioxidant activity can

Table 19. Immunomodulatory profile of *Tinospora cordifolia*[12,34,35]

Sl. No.	Part	Extract	Drug-induced (animal mode)	Dose (mg/kg)	Duration	Effect	Proposed mechanism
1	Root	Aqueous	Balb/c mice	200 and 500 µg/ml	2 weeks	Immunomodulating	The compounds TC-1, TC-2, TC-4, TC-5, TC-6 exhibited enhancement of IgG antibodies.
2	Stem	Aqueous	Male albino-20	--	--	Ameliorating immunosuppressive effects	Increases the phagocytosis capacity of peritoneal macrophages isolated from ccl4 intoxicated mice.
			1st group-5 albino	0.1ml sterile isotonic saline	15 days		
			2nd group-5 albino	0.5ml/kg CCl4 (i.p.)	Last 7 days		
			3rd group-5 albino	40mg/kg T.cordifolia extract orally	15 days		
			4rth group- 5 albino	40mg/kg T.cordifolia extract orally, CCl4 (i.p.)	T.cordifolia extract- 15 daysCCl4 (i.p.)- last 7 days		
3	Whole plant	Aqueous	Mice	100µl-injection	72h	Immunomodulatory effect	Primarily acts on the macrophages and stimulates the production of effector molecules.
4	Leaf	Ethanol	Fin Fish	0.8, 8, 80 mg/kg	3 weeks	Immunoprophylactic	Ethanol extract significantly enhanced neutrophil activity.
		Petro-leum	Fin Fish	0.8, 8, 80 mg/kg	3 weeks		Petroleum ether extract enhanced the secondary antibody response.
5	Whole Plant	Aqueous					
	In vitro						
	80 µg/ml						
	48 hours						
	Immuno-modu-latory effect	Macro-phage cell vi-ability.					
6	Stem	Alcoholic	Mice	12.5mg/kg in 500 µl saline – injection	72 hours	Immunomodulatory effect	Phagocytic activity.
	Stem						

Table 19. Continued…

	Alcoholic, aqueous						
	In vitro						
	100 µg/ml						
	Viability test -1 hour	Immuno-modulatory effect	Phagocytic activity on Polymorphonuclear cells (PMN Scale).				

Table 20. Phytochemical constituents responsible for antioxidant activity[42,80]

Sl. No.	Phytochemical constituents	antioxidant activity
1	**Cinnamaldehyde**	The primary active compound in cinnamon bark, recognized for its strong antioxidant properties.
2	Eugenol	A phenolic compound known for its strong free radical scavenging ability, contributing significantly to the antioxidant and anti-inflammatory properties of various plants, including cinnamon.
3	Cinnamic acid	A phenolic acid that contributes significantly to the overall antioxidant capacity of cinnamon, helping to neutralize free radicals and reduce oxidative stress.
4	Proanthocyanidins	Flavonoids that demonstrate strong antioxidant activity by donating hydrogen atoms to neutralize free radicals, thereby protecting cells from oxidative damage.

Table 21. Immunomodulatory functions of *Cinnamomum zeylanicum*

Sl. No.	Immunomodulatory functions	Details
1	Enhanced Phagocytic Activity	Occurs when the protection of immune cells from oxidative damage enables more efficient phagocytosis of pathogens, improving the body's ability to combat infections[78,80].
2	Cytokine Regulation	*Cinnamomum zeylanicum* reduces oxidative stress, thereby modulating cytokine production and promoting a balanced and effective immune response
3	Protection Against Immune Cell Apoptosis	Facilitated by the antioxidant properties of *Cinnamomum zeylanicum*, which help prevent oxidative stress-induced cell death, thereby preserving immune cell populations and ensuring sustained immune function[9,14,21].

Table 22. Mechanisms of antioxidant activity[15,81,96]

Sl. No.	Antioxidant Activity	Mechanism
1	Free Radical Scavenging	*Cinnamomum zeylanicum* contains bioactive compounds such as cinnamaldehyde, eugenol, and other phenolic derivatives, which are potent scavengers of free radicals. These compounds neutralize ROS and RNS, effectively reducing oxidative stress and preventing the damage to cellular structures that could compromise immune cell function.
2	Enhancement of Endogenous Antioxidant Enzymes	In addition to direct radical scavenging, *Cinnamomum zeylanicum* has been shown to enhance the activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These enzymes play a crucial role in neutralizing ROS and maintaining cellular homeostasis. By boosting their activity, *Cinnamomum zeylanicum* helps bolster the body's natural defense mechanisms against oxidative damage.
3	Reduction of Oxidative Stress and Inflammation	Chronic oxidative stress is often linked to inflammation, which can dysregulate immune responses and lead to chronic diseases. *Cinnamomum zeylanicum's* antioxidant properties help mitigate oxidative stress, thereby reducing the inflammatory cytokine production and promoting a balanced immune response. This antioxidant modulation is essential

Table 22. Continued…

		in preventing the overactivation or suppression of immune responses, which can lead to conditions like autoimmunity or immunodeficiency.
4	Inhibition of Lipid Peroxidation	Lipid peroxidation is a process in which free radicals attack lipids in cell membranes, resulting in cell damage and inflammation. *Cinnamomum zeylanicum* inhibits lipid peroxidation by neutralizing lipid radicals and stabilizing cell membranes. This helps preserve membrane integrity, which is essential for maintaining the proper function of immune cells.
5	Chelation of Metal Ions	Metal ions like iron and copper can catalyze the production of highly reactive hydroxyl radicals through the Fenton reaction. *Cinnamomum zeylanicum* contains compounds that chelate these metal ions, effectively preventing them from participating in reactions that generate reactive oxygen species (ROS).

influence the behaviour of immune cells, including macrophages, dendritic cells, and lymphocytes, enhancing their ability to detect and respond to pathogens. Furthermore, *C. zeylanicum* has been shown to modulate cytokine profiles, promoting an optimal balance between pro-inflammatory and anti-inflammatory mediators. This immunomodulatory action makes *C. zeylanicum* a promising candidate for addressing immune dysfunctions, including those involved in inflammatory diseases, autoimmune disorders, and immune senescence. The antioxidant activity of *C. zeylanicum* supports various aspects of immune function, including:

The antioxidant activity of *C. zeylanicum* plays a crucial role in its immunomodulatory effects. Scavenging free radicals, boosting antioxidant defences, and reducing inflammation caused by oxidative stress, it helps maintain the integrity and functionality of the immune system. This dual action in both antioxidant protection and immune modulation underscores the therapeutic potential of *C. zeylanicum* in addressing immune dysfunctions related to oxidative stress[96,97].

8.3.5 Antioxidant Properties of Cinnamon: Mechanisms and Implications in Disease Prevention

Spices and vegetables, particularly those rich in bioactive compounds, are renowned for their potent antioxidant activities, which can mitigate lipid peroxidation—a critical process involved in the pathogenesis of various human diseases, such as atherosclerosis and certain cancers[98]. Oxidative stress, stemming from an imbalance between reactive oxygen species (ROS) and the body's antioxidant defences, plays a significant role in inflammatory and immune responses, and its association with numerous diseases has made antioxidants a key focus of pharmacological research. *Cinnamomi cortex*, derived from *C. zeylanicum* (*Ceylon cinnamon*), stands out for its exceptionally high antioxidant concentration, with levels exceeding 75 mmol/100 g. This suggests that the therapeutic effects of the herb are largely mediated by its antioxidant properties[99]. Studies have demonstrated that water-alcohol extracts (1:1) of cinnamon inhibit lipoxygenase-dependent lipid peroxidation in vitro, a process that can cause cellular damage. Similarly, etheric, methanolic, and aqueous extracts of cinnamon effectively reduce oxidation in a beta-carotene/linoleic acid system, indicating a broad spectrum of antioxidant activity[100]. Notably, ethanol extracts from *Cinnamomum cassia* (Chinese cinnamon) dry bark showed superior inhibition of lipid peroxidation in rat liver homogenates when compared to alpha-tocopherol, a known antioxidant. These extracts also exhibited high superoxide anion scavenging activity and inhibited superoxide formation, further demonstrating their robust antioxidant potential. In addition to its effects on lipid peroxidation, cinnamon oil has been shown to exhibit Superoxide Dismutase (SOD)-like activity, which inhibits pyrogallol autoxidation catalyzed by the superoxide radical[101]. The volatile extracts from cinnamon, including essential oils, display moderate antioxidant activity across different assays, including aldehyde/carboxylic acid and conjugated diene tests. Several primary components of cinnamon oil—eugenol, (E)-cinnamaldehyde, and linalool — have also been tested for their antioxidant effects. Among these, eugenol and the essential oil demonstrated potent activities in reducing peroxynitrite-induced nitration and lipid peroxidation, whereas (E)-cinnamaldehyde

and linalool showed little to no activity in these models[102]. Furthermore, trans-cinnamaldehyde, derived from *Cinnamomum cassia*, was noted for its potent inhibition of nitric oxide (NO) production in RAW264.7 cells, with a corresponding decrease in the expression of inducible nitric oxide synthase (iNOS), highlighting its anti-inflammatory potential. While cinnamic acid and eugenol exhibited minimal activity in these assays, the antioxidant and anti-inflammatory activities of cinnamon's components are significant in modulating oxidative stress and immune function[103]. Additionally, flavonoids isolated from cinnamon bark have been tested for their free radical-scavenging potential using the DPPH radical scavenging assay[104]. The results confirmed the strong antioxidant activities of these compounds, as indicated by low inhibitory concentration (IC) values, high efficiency concentration (EC) values, and robust reducing power (ascorbic acid equivalents)[105]. These findings further corroborate the potent antioxidant activity of *C. zeylanicum*, which plays a crucial role in preventing oxidative damage and supporting overall immune health[106].

8.4 Immunomodulation of P. longum L.

The immunomodulatory and antioxidant mechanisms of *P. longum* (long pepper) have been extensively studied, revealing its potent effects on both innate and adaptive immune responses. *P. longum*, a traditional medicinal plant known for its diverse pharmacological properties, exerts significant immunostimulatory activity through various biochemical pathways and molecular mechanisms[45].

8.4.1 Immunomodulatory Mechanisms

Piper longum demonstrates its immunomodulatory effects primarily through the regulation of both specific and nonspecific components of the immune system (Table 23). The plant's active components, including piperine, have been shown to modulate haematological parameters, bone marrow cellularity, and the activity of immune cells. Studies conducted on Balb/c mice have highlighted the ability of *P. longum* extracts to increase white blood cell (WBC) counts, suggesting that it can stimulate the hematopoietic system and promote stem cell proliferation. The increase in WBCs also correlates with a rise in α-esterase-positive cells, indicating enhanced immune activity and a potent effect on the immune cell maturation process. Moreover, *P. longum* has been found to enhance the humoral immune response[32,35,38]. The plant extract increases the circulating antibody titer and promotes the production of plaque-forming cells, which are essential for antibody synthesis. This demonstrates that *P. longum* stimulates the production of antibodies, thus enhancing humoral immunity. The extract also plays a role in macrophage activation, increasing the macrophage migration index (MMI) and phagocytic index (PI), which boosts the host's resistance to infections and enhances its ability to neutralise pathogens. The immunomodulatory effects of *P. longum* are attributed to its diverse phytoconstituents, including alkaloids (such as piperine), glycosides, and saponins. These compounds are known to influence key immune cells, such as macrophages, neutrophils, lymphocytes, and natural killer (NK) cells, and modulate the production of cytokines and interleukins. By targeting various transcription factors and immune mediators, *P. longum* helps regulate immune responses, enhance antigen presentation, and reduce the phenomenon of apoptosis, all of which are crucial for maintaining immune system homeostasis[17,20,49].

8.4.2 Antioxidant Mechanisms

In addition to its immunomodulatory effects, *P. longum* also exhibits significant antioxidant properties, which contribute to its overall therapeutic potential. Oxidative stress is a key factor in many inflammatory and immune-related disorders, as reactive oxygen species (ROS) can damage cellular components such as DNA, proteins, and lipids, leading to cellular dysfunction. *P. longum* contains bioactive compounds like piperine, which have been shown to possess strong antioxidant activity. These compounds scavenge free radicals, thereby reducing oxidative damage and protecting immune cells from the harmful effects of oxidative stress. The antioxidant activity of *P. longum* is primarily mediated through the inhibition of lipid peroxidation and the enhancement of endogenous antioxidant enzymes (Table 24). These mechanisms help mitigate the effects of ROS and Reactive Nitrogen Species (RNS), which

Table 23. Mechanism of immunomodulatory effects of *Piper longum*[17,45,46]

Immunomodulatory Effects			
Sl. No.	**Mechanism**	**Pathways and Effects**	**Details**
1	*Hematopoietic System*	Stimulates WBC (white blood cell) production and bone marrow cellularity	Increases overall WBC count, suggesting activation of the hematopoietic system and stem cell proliferation, leading to enhanced immune responses.
2	*Humoral Immunity*	Enhances antibody production and circulating antibody titers	Increases plaque-forming cells, which are essential for antibody synthesis, thus boosting the humoral immune response.
3	*Macrophage Activation*	Increases macrophage migration and phagocytic activity	Improves the macrophage migration index (MMI) and phagocytic index (PI), promoting macrophage activity and enhancing the body's ability to clear pathogens.
4	*Cytokine Regulation*	Modulates cytokine production and interleukin levels	Influences immune cells like lymphocytes and NK cells, enhancing the release of pro-inflammatory cytokines for better immune responses.
5	*Apoptosis Regulation*	Reduces apoptosis in immune cells	Modulates programmed cell death (apoptosis) through transcription factor regulation, helping maintain immune cell viability during immune responses.

Table 24. Mechanism of antioxidant effects of *Piper longum*[45,46,48]

Antioxidant Effects			
Sl. No.	**Mechanism**	**Pathways and Effects**	**Details**
1	Free Radical Scavenging	Scavenges reactive oxygen species (ROS) and reactive nitrogen species (RNS)	Active compounds, such as piperine, neutralize free radicals, preventing cellular damage that can impair immune function.
2	Lipid Peroxidation Inhibition	Inhibits lipid peroxidation and cellular membrane damage	Active components reduce lipid oxidation, protecting immune cells from oxidative stress and improving immune cell function.
3	Endogenous Antioxidant Enzyme Activation	Enhances activity of endogenous antioxidant enzymes	Increases levels of enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which protect immune cells from oxidative damage.
4	Superoxide Radical Scavenging	Exhibits superoxide dismutase (SOD)-like activity	Piperine and other compounds reduce the harmful effects of superoxide radicals, protecting cellular structures involved in immune responses.
5	Protection of Immune Cells	Reduces oxidative stress in immune cells	Protects immune cells (e.g., macrophages and lymphocytes) from oxidative damage, improving their function in immune surveillance and pathogen defense.

are known to interfere with immune cell function. By reducing oxidative stress, *P. longum* enhances immune cell functionality, improves the phagocytic capacity of macrophages, and promotes the overall health and efficiency of the immune system[16,50].

Piper longum is a potent immunomodulator that influences both innate and adaptive immunity, enhancing the body's defence mechanisms. The plant's active constituents, including piperine, work synergistically to increase WBC counts, promote stem cell proliferation, and stimulate the production of antibodies. Furthermore, the antioxidant properties of *P. longum* contribute to its ability to mitigate oxidative stress, protecting immune cells from damage and improving immune function. The combination of these mechanisms positions *P. longum* as a valuable natural product for immune system enhancement, with promising applications in the prevention

Table 25. (a) Traditional and (b) therapeutic applications of *Withania somnifera*

(a) Traditional Applications		
Sl. No.	**Category**	**Application**
1	General Tonic	In *Ayurvedic* medicine, Ashwagandha is classified as a "*rasayana*" (rejuvenative tonic), traditionally used to enhance vitality, strength, and overall well-being. It is used to promote longevity and is often included in formulations aimed at improving general health.
2	Adaptogen	Ashwagandha is widely used as an adaptogenic herb, helping the body adapt to stress and environmental challenges. It is traditionally believed to support resilience and reduce the effects of mental and physical stress, promoting balance and tranquility.
3	Immunity Booster	In traditional medicine, *Withania somnifera* is known for its immune-boosting properties. It has been used to improve immune function, support recovery from illnesses, and reduce the duration of infections.
4	Sleep Aid	Ashwagandha is traditionally used to address sleep disturbances, often being prescribed as a remedy for insomnia and anxiety-related sleep issues. It is thought to calm the nervous system and promote restorative sleep.
5	Anti-inflammatory and Pain Relief	Ashwagandha has been used to relieve symptoms of inflammation, pain, and joint disorders. It is traditionally applied in conditions such as arthritis and muscle stiffness[1,7,24].
(b) Therapeutic Applications		
1	Stress and Anxiety Management	Modern research supports the traditional use of *Withania somnifera* as an anti-stress agent. Studies have shown that the herb can significantly reduce cortisol levels (a stress hormone), thus reducing stress and anxiety.
2	Neuroprotective Effects	*Withania somnifera* has demonstrated neuroprotective effects, helping to protect against neurodegenerative diseases like Alzheimer's and Parkinson's disease. It is believed to enhance cognitive function, improve memory, and slow down the aging of brain cells.
3	Anti-cancer Properties	Some studies have suggested that Ashwagandha possesses anticancer properties, inhibiting the growth of cancer cells, reducing tumor size, and protecting healthy cells from chemotherapy-induced damage. Its withanolides are thought to play a role in inducing apoptosis (cell death) in cancer cells96,108,109.
4	Anti-inflammatory Effects	Ashwagandha contains several compounds that exhibit anti-inflammatory activity. It has been shown to alleviate conditions associated with chronic inflammation, such as rheumatoid arthritis, by inhibiting inflammatory cytokines and oxidative stress.
5	Antioxidant Activity	The herb is known for its potent antioxidant properties, which help neutralize free radicals in the body. This may contribute to its effectiveness in preventing or managing age-related diseases and oxidative stress-related conditions.
6	Endocrine Health	Ashwagandha has shown promise in balancing hormone levels, particularly thyroid and adrenal hormones. It has been used to help manage hypothyroidism and adrenal fatigue.
7	Blood Sugar Regulation	Clinical studies have suggested that *Withania somnifera* can help regulate blood sugar levels, making it a potential adjunct therapy for managing type 2 diabetes. Its active compounds are believed to enhance insulin sensitivity and lower blood glucose levels.
8	Reproductive Health	Ashwagandha has been traditionally used to enhance fertility in both men and women. It is thought to improve sperm quality in men, as well as increase libido and sexual function in both genders[4,23,53,110].

Table 26. (a) Traditional and (b) therapeutic applications of *Tinospora cordifolia*

(a) Traditional Applications		
Sl. No.	**Category**	**Application**
1	Rejuvenation (*Rasayana*)	*Tinospora cordifolia* is categorized as a "*rasayana*" in *Ayurveda*, traditionally used to rejuvenate the body, improve vitality, and delay aging[108,109].
2	Immune Enhancement	Traditionally referred to as "*Amrita*" (nectar of immortality), it is widely used to enhance immunity and promote resilience against infections.
3	Antipyretic (Fever Management)	Known as a natural febrifuge, *Tinospora cordifolia* has been used for managing recurrent fevers, including malaria and dengue.
4	Liver Support	In traditional systems, it is used as a hepatoprotective agent to detoxify and strengthen liver function.
5	Diabetes Management	*Guduchi* has been traditionally recommended to manage blood sugar levels and is included in formulations for diabetes in *Ayurvedic* medicine.
6	Digestive Aid	It has been used to relieve indigestion, improve appetite, and manage gastrointestinal disorders, including hyperacidity and flatulence.
7	Anti-inflammatory Use	Traditionally, *Tinospora cordifolia* has been used for conditions like arthritis and gout to alleviate inflammation and joint pain[34,36,69].
8	Skin Disorders	Decoctions made from *Tinospora cordifolia* are applied or consumed for skin diseases, wounds, and conditions like eczema and psoriasis.
(b) Therapeutic Applications		
1	Immunomodulation	Modern studies confirm *Tinospora cordifolia* 's ability to modulate the immune system. It enhances the activity of macrophages and other immune cells, making it effective against infections and autoimmune conditions.
2	Antioxidant Properties	*Tinospora cordifolia* is rich in antioxidants, which help in neutralizing free radicals, protecting cells from oxidative stress, and reducing the risk of chronic diseases.
3	Antidiabetic Effects	Studies indicate that *Tinospora cordifolia* can lower blood glucose levels by improving insulin sensitivity. It also aids in reducing complications associated with diabetes, such as oxidative stress and inflammation.
4	Anti-inflammatory and Antipyretic Effects	The herb has demonstrated potent anti-inflammatory properties, making it effective for conditions like rheumatoid arthritis. Its antipyretic activity helps reduce fever by lowering inflammatory markers.
5	Hepatoprotective Activity	*Tinospora cordifolia* protects the liver from damage caused by toxins, alcohol, and medications. It aids in regenerating liver cells and improving liver enzyme profiles[12,63].
6	Adaptogenic and Stress-Relief Effects	As an adaptogen, *Guduchi* helps the body cope with stress by modulating cortisol levels. This property supports mental clarity and overall resilience.
7	Antimicrobial Properties	It exhibits antibacterial, antiviral, and antifungal activities, making it useful for treating infections like urinary tract infections, respiratory conditions, and skin infections.
8	Anti-cancer Potential	Research indicates that *Tinospora cordifolia* exhibits anti-tumor activity by inducing apoptosis (programmed cell death) in cancerous cells and preventing the proliferation of tumors.
9	Neuroprotective Effects	*Tinospora cordifolia* supports cognitive health by improving memory and reducing neuroinflammation, showing promise for managing neurodegenerative diseases like Alzheimer's.
10	Cardiovascular Benefits	The herb helps regulate blood pressure, reduces cholesterol levels, and protects the heart from oxidative damage.
11	Anti-anemic Properties	It is known to improve hemoglobin levels and support recovery from anemia by enhancing iron metabolism[94].
12	Antiallergic Effects	*Guduchi* is effective in managing allergic conditions, such as asthma and rhinitis, due to its anti-inflammatory and immune-balancing actions.

Table 27. (a) Traditional and (b) therapeutic applications of *Cinnamomum zeylanicum*

(a) Traditional Applications		
Sl. No.	**Category**	**Application**
1	Digestive Health	Cinnamon has been traditionally used as a carminative to alleviate bloating, indigestion, and flatulence. It is often included in remedies for gastrointestinal discomfort[107,111,113].
2	Respiratory Ailments	In *Ayurveda*, cinnamon is used to manage respiratory conditions like colds, coughs, and bronchitis due to its warming and expectorant properties.
3	Menstrual Health	Cinnamon has been employed to regulate menstrual cycles and reduce menstrual cramps.
4	Fever and Infections	Traditional healers used cinnamon to reduce fevers and combat infections, capitalizing on its antimicrobial properties.
5	Diabetes Management	Traditional medicine includes cinnamon as a remedy for regulating blood sugar levels and enhancing insulin activity.
6	Aphrodisiac	It is considered a warming spice that boosts libido and vitality in both men and women.
7	Wound Healing	Powdered cinnamon bark and oil are used in traditional remedies for wound care due to their antiseptic properties[14,41].
8	Flavor and Preservation	Cinnamon's aromatic and antimicrobial qualities made it a popular choice for flavoring foods and preserving perishables[80,112].
(b) Therapeutic Applications		
1	Antidiabetic Properties	Studies have confirmed cinnamon's ability to lower blood glucose levels by improving insulin sensitivity. It also reduces fasting blood sugar and postprandial glucose spikes[110].
2	Antimicrobial Activity	*Cinnamomum zeylanicum* demonstrates significant antibacterial, antifungal, and antiviral activities, making it effective against pathogens like *E. coli, Candida albicans*, and *Helicobacter pylori*.
3	Anti-inflammatory Effects	Cinnamaldehyde, a primary component of cinnamon essential oil, inhibits pro-inflammatory markers, providing relief in conditions like arthritis and inflammatory bowel diseases[114].
4	Cardiovascular Benefits	Cinnamon aids in reducing cholesterol levels, lowering triglycerides, and improving heart health. Its antioxidant properties help prevent atherosclerosis.
5	Antioxidant Properties	Rich in polyphenols, *Cinnamomum zeylanicum* neutralizes free radicals, protecting cells from oxidative damage and reducing the risk of chronic diseases.
6	Cognitive Support	Cinnamon has shown neuroprotective potential, with studies indicating improved memory and reduced neuroinflammation, beneficial for conditions like Alzheimer's and Parkinson's[95].
7	Weight Management	Cinnamon is often included in weight-loss regimens for its ability to regulate blood sugar, improve metabolism, and suppress appetite.
8	Anticancer Potential	Bioactive compounds in cinnamon, such as cinnamaldehyde and eugenol, have demonstrated anti-tumor activity by inducing apoptosis and inhibiting cancer cell proliferation.
9	Antimicrobial in Food Preservation	Cinnamon is widely used in the food industry as a natural preservative, preventing microbial contamination and spoilage.
10	Dental Care	Cinnamon's antibacterial properties make it effective against oral pathogens, reducing bad breath and preventing dental caries.
11	Skin Health	Cinnamon oil is used topically for conditions like acne, eczema, and fungal infections due to its antimicrobial and anti-inflammatory effects.
12	Antiulcer Activity	Cinnamon extracts protect the gastric mucosa and reduce the risk of ulcers, particularly those induced by *H. pylori* or non-steroidal anti-inflammatory drugs (NSAIDs).
13	Immune Modulation	Regular use of cinnamon strengthens the immune system, aiding the body in fighting infections and reducing chronic inflammation.
14	Respiratory Benefits	Inhalation or consumption of cinnamon oil helps alleviate congestion, soothe sore throats, and manage seasonal allergies.
15	Stress Relief	Cinnamon's essential oil is used in aromatherapy for its calming effects, which help reduce anxiety and stress[52].

Table 28. (a) Traditional and (b) therapeutic applications of *Piper longum*

(a) Traditional Applications			
Sl. No.	**Category**	**Application**	**Details**
1	Digestive Health	Used as a carminative, digestive aid, and to relieve indigestion	Traditionally used to enhance digestion and alleviate bloating, constipation, and dyspepsia, acting as a digestive stimulant[20].
2	Respiratory Health	Used to treat asthma, cough, bronchitis, and other respiratory disorders	*Piper longum* is believed to relieve respiratory symptoms by reducing inflammation, clearing mucus, and acting as an expectorant.
3	Pain and Inflammation	Relieves pain, inflammation, and fever	Used in traditional medicine for its anti-inflammatory properties to treat conditions like arthritis, muscular pain, and fever.
4	Aphrodisiac	Traditionally used as an aphrodisiac to enhance sexual function	Believed to improve libido and sexual performance by stimulating circulation and energy levels[16].
5	Anti-venom	Used as a remedy for snakebites and insect stings	Traditionally applied in cases of venomous bites or stings, believed to counteract toxins and reduce symptoms.
6	Antimicrobial	Used for its antimicrobial properties in treating infections	Utilized to treat common ailments like cold, flu, and infections, with its antibacterial, antiviral, and antifungal properties[83].
(b) Therapeutic Applications			
1	Immunomodulation	Enhances immune response, acting as an immunostimulant	Boosts both innate and adaptive immune systems, enhancing white blood cell production, macrophage activity, and antibody production.
2	Antioxidant Effects	Reduces oxidative stress and prevents cellular damage	Neutralizes free radicals, protecting cells and tissues from oxidative damage, improving cellular function, and delaying aging[17,45].
3	Anti-inflammatory	Reduces inflammation and inflammation-related conditions	Effective in treating inflammatory diseases like arthritis, gout, and inflammatory bowel disease (IBD) by modulating cytokine production and oxidative stress.
4	Respiratory Support	Treats asthma, bronchitis, and cough	Reduces airway inflammation and mucus production, acting as a bronchodilator and expectorant in respiratory conditions.
5	Digestive Health	Enhances digestion and alleviates gastrointestinal disorders	Stimulates digestive enzymes, alleviates bloating, and acts as a laxative, improving gut health and digestion[16,49].
6	Neuroprotection	Protects against neurodegenerative diseases	Shows potential in preventing neurodegenerative diseases like Alzheimer's and Parkinson's through its antioxidant and anti-inflammatory properties.
7	Cancer Therapy	Potential role in cancer treatment	Contains compounds such as piperine, which may have anticancer properties, inhibiting tumor growth and metastasis through modulation of cell signaling pathways.
8	Anti-diabetic	Helps manage blood sugar levels	Exhibits potential anti-diabetic effects by improving insulin sensitivity and glucose uptake in the body.
9	Liver Health	Promotes liver detoxification and protects against liver damage	Used in liver diseases such as hepatitis and cirrhosis by promoting detoxification and protecting liver cells from oxidative damage[47,50].

and management of various immune-related conditions[49,50,83].

9. Applications

There are several Traditional and Therapeutic Applications of *W. somnifera* (Table 25), *T. cordifolia* (Table 26), *Cinnamomum zeylanicum* (Table 27) *and P. longum* (Table 28). They are discussed in the following:

10. Conclusion

The comprehensive review of *W. somnifera* (L.) Dunal, *T. cordifolia* (Willd.) Miers, *C. zeylanicum* Blume (synonym: *C. verum* J.Presl), and *P. longum L.* underscore their profound immunomodulatory, antioxidant, and therapeutic potential, as well as their deep-rooted significance in traditional medicine. These plants are not only revered for their historical applications but also stand as promising candidates for modern pharmacological research due to their diverse bioactive compounds and multifaceted health benefits. Collectively, they offer a natural avenue for managing various chronic and acute conditions, including oxidative stress, immune dysfunction, and metabolic disorders. *W. somnifera (Ashwagandha)* has long been celebrated for its adaptogenic, anti-inflammatory, and antioxidant properties, addressing ailments ranging from stress and fatigue to chronic diseases like arthritis and cancer. The plant's bioactive compounds, particularly withaferin A, exhibit potent immunostimulatory activity, enhancing the functions of immune cells such as macrophages and dendritic cells. Despite this, there remain gaps in understanding the precise molecular pathways through which these effects are mediated. Addressing these knowledge gaps, alongside conducting more extensive clinical trials, is essential for optimising its therapeutic applications and ensuring its safe integration into clinical practice. *T. cordifolia (Guduchi)* is another pivotal plant with extensive immunomodulatory and antioxidant capabilities. Its active constituents enhance both innate and adaptive immunity, making it an ideal candidate for managing immune-related conditions. Additionally, its ability to combat oxidative stress by neutralising free radicals highlights its potential as a protective agent against chronic diseases like diabetes and cancer. However, further research is necessary to identify the specific molecular mechanisms and bioactive compounds responsible for these effects, as well as to explore their role as an adjunctive therapy in oncology. *C. zeylanicum (Ceylon cinnamon)* offers significant contributions to immunomodulation and oxidative stress reduction through compounds such as cinnamaldehyde, eugenol, and cinnamic acid. These bioactives have demonstrated the ability to prevent lipid peroxidation, scavenge reactive oxygen species, and modulate immune responses. This positions cinnamon as a potential therapeutic for conditions such as diabetes, cardiovascular diseases, and cancer. Nonetheless, most of the current evidence is derived from preclinical studies, emphasising the need for robust clinical trials to validate its efficacy and safety in humans. Furthermore, distinguishing the pharmacological effects of different cinnamon species (*e.g.*, *C. zeylanicum* vs. *C. cassia*) remains crucial for its standardised use. *Piper longum* (Long Pepper), an equally significant plant in traditional medicine, completes this quartet of potent botanicals. Known for its immunomodulatory, antioxidant, and anti-inflammatory properties, *P. longum* is widely used in treating respiratory ailments, digestive disorders, and chronic conditions such as arthritis and diabetes. Its key bioactive compound, piperine, enhances the bioavailability of other therapeutic agents, making it a valuable adjunct in polyherbal formulations. Additionally, *P. longum* demonstrates potential in modulating both innate and adaptive immune responses, while its antioxidant activity offers protection against cellular damage caused by oxidative stress. Future research should focus on elucidating the mechanisms behind its effects and exploring its synergistic potential in combination therapies.

The synergistic potential of *W. somnifera* (L.) Dunal, *T. cordifolia* (Willd.) Miers, *C. zeylanicum* Blume (synonym: *C. verum* J.Presl), and *P. longum L.* underscore their promise in addressing a spectrum of health challenges. While traditional medicine has provided a solid foundation for their therapeutic use, modern scientific validation is imperative to establish standardised dosages, safety profiles, and efficacy through human trials. By bridging the gap between traditional knowledge and contemporary research, these plants can contribute significantly to developing novel and holistic approaches to health and wellness.

11. Future Scope

The future of immunomodulatory research on medicinal plants such as *W. somnifera* (L.) Dunal, *T. cordifolia* (Willd.) Miers, *C. zeylanicum* Blume (synonym: *C. verum* J.Presl), and *P. longum L.* are vast and exciting, offering numerous opportunities for advancing their therapeutic applications. The following areas of exploration are pivotal for maximising their clinical potential.

11.1 Molecular Mechanism Studies

While the immunomodulatory effects of plants like *W. somnifera*, *T. cordifolia*, *C. zeylanicum*, and *P. longum* have been established, their underlying molecular mechanisms are not fully understood. Future research should focus on identifying and elucidating the signalling pathways triggered by bioactive compounds such as withaferin A in *W. somnifera*, piperine in *P. longum*, and other key constituents. This would enable a deeper understanding of how these plants interact with the immune system at a cellular and molecular level, potentially unveiling new targets for therapeutic interventions.

11.2 Standardisation and Dosage Optimisation

A major limitation in the clinical use of these herbal medicines is the absence of standardised dosages and formulations. Variability in plant constituents, extraction methods, and product quality may affect their efficacy and safety. Research should aim to standardise the preparation of plant-based extracts, focusing on the optimal doses of active components such as piperine, withaferin A, and alkaloids from *T. cordifolia*. Moreover, the development of robust guidelines for dosage forms and administration could improve clinical outcomes and minimise adverse effects[95,114].

11.3 Clinical Trials and Validation

Despite promising preclinical evidence, more randomised controlled trials (RCTs) are essential to confirm the efficacy and safety of these plants in humans. Future clinical trials should target a range of health conditions where immune modulation is crucial, including autoimmune diseases, inflammatory disorders, and cancer. Additionally, biomarkers of immune function, oxidative stress, and disease progression should be measured to assess the therapeutic impact of these plants. By rigorously testing the clinical relevance of these botanicals, their integration into conventional medicine could be more seamlessly achieved.

11.4 Synergistic Effects and Polyherbal Formulations

The therapeutic potential of *W. somnifera*, *T. cordifolia*, *C. zeylanicum*, and *P. longum* may be further amplified through combinations with other herbal or pharmaceutical agents. The synergistic effects of these plants in polyherbal formulations could enhance therapeutic efficacy, reduce individual dosages, and minimise side effects. Investigating the synergistic properties of plant combinations in clinical trials will be crucial for optimising treatment protocols[115].

11.5 Long-term Safety and Drug Interactions

Although these plants are generally regarded as safe, comprehensive long-term safety data are lacking, particularly concerning their use alongside conventional pharmaceutical drugs. Further research should focus on understanding potential herb-drug interactions, especially in individuals with pre-existing conditions or those on chronic medication. Evaluating the pharmacokinetics and pharmacodynamics of these plants in combination with modern medicines is vital to ensure safe and effective therapeutic regimens[108,116].

11.6 Exploration of New Therapeutic Applications

The scope of these plants extends beyond immunomodulation. Given the promising anti-inflammatory, antioxidant, and adaptogenic properties of *W. somnifera*, *T. cordifolia*, *C. zeylanicum*, and *P. longum*, exploring their potential in other therapeutic areas, such as neurodegenerative diseases (*e.g.*, Alzheimer's and Parkinson's), metabolic disorders, and chronic infections, is warranted. Their ability to influence the immune system and combat oxidative stress positions these plants as potential adjuncts in treating a wide range of conditions.

Withania somnifera, *T. cordifolia*, *C. zeylanicum*, and *P. longum* already hold substantial promise

as immunomodulatory and therapeutic agents; substantial research efforts are needed to optimise their clinical application. By addressing the challenges of molecular mechanism elucidation, standardisation, clinical validation, and long-term safety, these plants could become integral components of modern medicine, enhancing the effectiveness of treatments and offering novel therapeutic avenues for a wide range of diseases[25,30,109,117].

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13. Author Contribution

R.P. conceptualized the review, conducted the literature survey, and drafted the manuscript. B.C. provided critical revisions, supervised the work, and approved the final version for submission. Both authors read and approved the final manuscript.

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