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Review Article

Harītakī (*Terminalia chebula*) as an Immunomodulator: Evidence from Āyurveda and Contemporary Biomedical Research

Dr. Tanuja Sagar[1], Dr. Unnikrishnan S.[2], Dr. Rohit Mandal[3]

[1] P.G. Scholar, Department of Swasthavritta & Yoga, Ch. Brahm Prakash Ayurved Charak Sansthan (CBPACS), New Delhi. ORCID: https://orcid.org/0009-0001-2314-4803
[2] Professor & Head, Department of Swasthavritta & Yoga, Ch. Brahm Prakash Ayurved Charak Sansthan (CBPACS), New Delhi. ORCID: https://orcid.org/0009-0002-4091-3392
[3] P.G. Scholar, Department of Swasthavritta & Yoga, Ch. Brahm Prakash Ayurved Charak Sansthan (CBPACS), New Delhi. ORCID: https://orcid.org/0009-0009-3542-3082

Abstract

Introduction: This paper explores the immunomodulatory potential of Terminalia chebula (Harītakī), a revered herb in Āyurveda known for its multifaceted health benefits. Classified as a Rasāyana, Harītakī is praised for its rejuvenating properties in classical texts. The present work synthesizes findings from traditional literature and modern research to elucidate Harītakī's impact on the immune system through its diverse pharmacological actions. The review examines Harītakī's ability to enhance both cellular and humoral immunity, supported by evidence of increased lymphocyte proliferation, elevated antioxidant enzyme levels, and modulation of cytokine production. Furthermore, the study investigates its therapeutic efficacy against specific diseases and its potential as an adjunct therapy in conditions such as diabetes and amoebiasis. Contemporary research has identified its major phytochemical constituents, including chebulic acid, gallic acid, chebulagic acid, triterpenoids, and anthraquinones.[1] These findings underscore Harītakī's significance as an immunostimulant and highlight its broader applications in promoting overall health and combating immune-related disorders.

Methods: Classical Āyurvedic literature—including the Caraka Saṃhitā, Suśruta Saṃhitā, and Bhāvaprakāśa Nighaṇṭu—along with modern scientific articles related to Harītakī, were reviewed. Relevant data were extracted and analysed to assess Harītakī's role as an immunomodulator.

Result: A review of classical texts and contemporary scientific evidence suggests that Harītakī exhibits significant immunomodulatory effects. Its ability to balance all three doṣas, enhance Ojas and Agni, and provide robust antioxidant activity is supported in both traditional and modern sources.

Discussion: Harītakī is considered a potent Rasāyana herb for supporting longevity and enhancing resistance to disease. Classical literature often refers to it by honorific titles such as the "king of medicine," reflecting its wide-ranging therapeutic benefits.[2] The combined classical and modern evidence reinforces Harītakī's relevance as a natural immunomodulator.

Keywords: Rasāyana, Immunomodulator, Harītakī, Vyādhikṣamatva, Terminalia chebula, Phytochemicals, Antioxidant activity.

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Address for Correspondence:
Dr. Tanuja Sagar, P.G. Scholar, Department of Swasthavritta & Yoga, Ch. Brahm Prakash Ayurved Charak Sansthan (CBPACS), New Delhi, Email ID: drtanujasagar@gmail.com

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Introduction

"Health is the soul that animates all the enjoyments of life, which fade and are tasteless without it." (Seneca).[3] That is the prime objective mentioned in Āyurveda

“Svasthasya Svāsthya Rakṣaṇa”. To maintain excellent health Āyurvedic texts mention lots of therapies and drugs. One of the famous is Rasāyana therapy. Rasāyana is one of the eight divisions of Āyurveda. Rasāyana therapy enriches rasa with nutrients to help one attain longevity, memory, intelligence, health, youthfulness, excellence of lustre, complexion, and voice, optimum development of the physique and sense organs, mastery over phonetics, respectability, and brilliance. In Sanskrit, Rasāyana means "path of essence".[4]

The word Rasāyana is derived from two root words, 'rasa' and 'ayana.' The first root word, *rasa* refers to the first of the seven dhātus. This substance is derived primarily from food and contains all the nutrients required by various tissues. It also could refer to the ojas – which constitute the essence of all seven dhātus and form the seat of a vital life force. The second root word 'ayana' refers to circulation in general. Furthermore, '*ayana*' denotes three more purposeful meanings, viz.,

1. Kham (space),
2. Srotas (channels/vessels), and
3. Mārga (way).

Thus, '*ayana*' could be interpreted as a highly dynamic process, which keeps all the vital processes on the move, enriches the body with the best forms of dhātus, and prevents degenerative processes.

According to Ācārya Caraka, the use of Rasāyana results in longevity (*dīrghāyu*), memory (*smṛti*), intellect (*medhā*), freedom from diseases (*ārogya*), youth (*taruṇa-vaya*), complexion (*varṇa*), and voice (*svara*), the excellent potentiality of the body (*deha-bala*) and the sense-organs (*indriya-bala*), vāk-siddhi (i.e. what he says comes true), respect and brilliance.[5]

Rasāyana drugs are believed to slow down the aging process (jarā) and provide a defence mechanism against diseases (vyādhi). Rasāyana also improves the host resistance (*vyādhikṣamatva*) of an individual, helping to prevent aging and diseases. Specific diets and lifestyle changes are also advised in Rasāyana therapy. Rasāyana drugs also act on the immune system and the immune system has connections with several other organs and can directly or indirectly influence the actions of many other organs. Rasāyana shows myriad actions on other organs by acting on the immune system. Different varieties of Rasāyana are mentioned in Āyurveda:

- Medhya Rasāyana (nootropic),
- Naimittika Rasāyana (promoter of specific vitality in specific diseases),
- Ājasrika Rasāyana (dietary Rasāyana), and
- Ācāra Rasāyana (conduct-based Rasāyana).[6]

In Āyurveda, Harītakī's effects are described through its general properties like being a rejuvenator and disease conqueror, while modern science identifies specific immunomodulatory mechanisms, such as modulating cytokines and immune cells to combat inflammation and infection. Harītakī boosts overall immunity to increase vitality and longevity and modulates the function of immune cells such as CD4+ and CD8+ T cells, and enhances natural killer (NK) cell activity. Harītakī also focuses on restoring balance to the body through its inherent qualities, and its bioactive compounds interact with targets like cytokines, signalling pathways, and immune cells.

Materials and Method:

This study is narrative review synthesizing classical Āyurvedic literature and modern research findings on Harītakī's immunomodulatory effect.

Methodology structure:

- Āyurvedic literature review (*Caraka Saṃhitā*, *Suśruta Saṃhitā* and *Bhāvaprakāśa*)
- Modern research insights (PubMed, Google Scholar and AYUSH Research Portal)
- Immunomodulatory mechanism (Antioxidant, Immunomodulator activity)
- Phytochemicals in Harītakī

Material has been collected from ancient Āyurvedic texts, research journals and electronic databases.

Harītakī

Harītakī (*Terminalia chebula* Retz) as a Rasāyana is mentioned in the Laghutrayī – Bhāvaprakāśa (anti-aging). In *Caraka Saṃhitā*, *Cikitsāsthāna*, Abhayā–Āmalakīya Rasāyana-pāda, properties of Harītakī are described as possessing all the six rasas excluding *lavaṇa*; it is hot, beneficial, carminative, light, appetizer, digestive, life-promoting, tonic, excellent sustainer of youthful age, alleviates all diseases and provides strength to all the sense organs.[7]

In Tibetan medicine, Harītakī is known as A-ru-ra and praised with the adjective Sman-mchog-rgyal-pa, meaning the "King of medicines".[8]

Immunity:

The immune system's primary defense mechanism is its ability to identify and eliminate non-self entities. Through a complex regulation of humoral and cellular factors, the system functions throughout the body. The immune

system's protective function, which begins with the identification of non-self bodies and substances, places it in a crucial position between the host's healthy and diseased states. The immune system is composed of many interdependent cell types that collectively protect the body from bacterial, parasitic, fungal, viral infections and from the growth of tumor cells. Many of these cell types have specialized functions. The cells of the immune system can engulf bacteria, kill parasites or tumor cells, or kill viral infected cells. Often, these cells depend on the T helper subset for activation signals in the form of secretions formally known as cytokines, lymphokines, or more specifically interleukins.[9]

Immunomodulator:

An immunomodulator is a drug used for its effects on the immune system. It can be defined as a substance, which can influence any component or function of the immune system in a specific or non-specific way. The concept of immunomodulation is mentioned as Rasāyana in Āyurveda. Āyurveda has two aims: the first is the prevention and promotion of health and the second is a cure for the disease. Rasāyana is used for both aims.[10]

"Immunomodulation" means altering an immune response, which may increase or decrease the immune responsiveness. Enhancing immune responsiveness is called immunostimulation, and reducing immune responsiveness is called immunosuppression. An immunomodulator may be defined as a substance, biological or synthetic, which can stimulate, suppress, or modulate any of the components of the immune system including both innate and adaptive arms of the immune response. The essence of immunomodulation is that a pharmacological agent acting under various dose and time regimens displays an immunomodulating effect.[11]

The immune system is multi-layered, with defences on several levels. Most elementary is the skin, which serves as the first barrier to infection. Another barrier is physiological, where pH and temperature provide inappropriate living conditions for foreign organisms. Once pathogens have entered the body, they are dealt with by the innate immune system and by the acquired or adaptive immune system. Both systems comprise numerous cells and molecules that interact in a complex manner to detect and eliminate pathogens. Both detection and elimination depend upon chemical bonding: surfaces of immune system cells are covered with various receptors, some chemically bind to pathogens, and some bind to other immune system cells or molecules to enable the complex

system of signalling that mediates the immune response.[12]

Molecular immunomodulation primarily operates by regulating key signaling pathways and transcription factors such as NF-κB and AP-1, which control cytokine production and immune cell activation. It also involves modulation of pathways like STING and AKT/PKB, affecting processes like inflammation, T cell activation, and immune tolerance. By influencing molecules such as cytokines, immune checkpoints (e.g., PD-1, CTLA-4), and enzymes like IDO, immunomodulators can either enhance immune defense or suppress excessive inflammation. The implications of these mechanisms include the ability to fine-tune immune responses for therapeutic aims—boosting immunity against infections and cancer or dampening it in autoimmune diseases and chronic inflammation. This molecular control ensures immune balance, preventing harmful overactivation while enabling effective defense, forming the basis of modern immunotherapies. Thus, molecular immunomodulation's role in precisely controlling immune pathways holds significant promise for targeted treatments across various diseases.[13]

Classical Text View of Harītakī:

Āyurvedic classics have attributed recana (laxative), lekhanā (scraping), medhyā (intellect promoter), netrya (beneficial for vision), dīpana (appetizer), pācana (digestive), vāta-anulomaka (carminative), hṛdya (cardiotonic), indriya-prasādana (nurturing the sense organ), āyuṣya (healthy long life), bṛhmaṇīya (nourishing the body), vaya sthāpana (anti-aging), Rasāyana (rejuvenating), bala–buddhi–smṛti-vardhaka (promotes physical strength, intellect, and memory), śothahara (anti-inflammatory), vedanāhara (analgesic), vraṇa-śodhana–ropaṇa (wound cleansing and healing) properties to it.[8]

Bhāvaprakāśa has described different methods of using Harītakī to attain different actions. When it is chewed, it enhances digestive fire; when used after rubbing on stone, it acts as mala-śodhana (cleanses toxins); when used after boiling, it acts as saṃgrāhī (absorbent); and when it is used after frying, it becomes tridoṣa-śāmaka (pacify tridoṣas). When Harītakī is taken with food, it enhances buddhi, bala, and indriya, pacifies tridoṣas, and dispels mala, mūtra, and other toxins. When it is taken after food, it readily cures digestive disorders and pacifies diseases of vāta, pitta, and kapha. To pacify vāta disorders, Harītakī should be used with ghṛta (ghee), in pitta disorders with śarkarā (sugar), in kapha disorders with lavaṇa (salt), and in all other diseases with guḍa.[7]

Characteristics of Best Quality Harītakī (Bhāvaprakāśa):

It should be navā (fresh), snigdha (smooth), ghana (bulky), vṛttā (ovoid shape), guru (heavy), should drown when dipped in water, and weigh about two karṣa, i.e., equal to the weight of two Bibhitakī fruits (approx. 20 g). This type of Harītakī is considered the best for medicinal usage.[8]

Pharmacological Actions

The fruit has multiple pharmacological and medicinal activities such as astringent, laxative, digestive, carminative, anthelmintic, antiulcer, antispasmodic, antioxidant, antimicrobial, antiviral, antiseptic, anti-inflammatory, anti-cancerous, antiaging, aphrodisiac, diuretic, purgative, radioprotective, antidiabetic, hepatoprotective, cardioprotective, blood purifier, cytoprotective, antiarthritic, hypolipidemic, adaptogenic, immunomodulator, and wound-healing activity.[14]

Immune Enhancement:

Harītakī has been shown to stimulate both humoral and cellular immunity. Animal studies have demonstrated that aqueous extracts of Harītakī increase white blood cell (WBC) counts, promote lymphocyte proliferation, and enhance antibody production, thereby reflecting improved immune defense mechanisms.[15] Its immunomodulatory activity is attributed to the presence of compounds such as tannins, flavonoids, gallic acid, and chebulagic acid, which also confer it strong antioxidant properties.[16]

Antioxidant Activity

Harītakī is a powerful antioxidant. It scavenges free radicals, reducing oxidative stress on immune cells. Antioxidants neutralize reactive oxygen species, reduce inflammation, and help regulate cytokine levels—vital for healthy immune function. This helps maintain the integrity and function of lymphocytes, macrophages, and other key components of the immune system.[17]

Anti-cancerous

Methanol extracts of Harītakī have shown the ability to induce apoptosis (programmed cell death) in various cancer cell lines, including prostate, breast, and colon cancer, and to inhibit tumour growth. This is primarily attributed to its powerful antioxidant and anti-proliferative constituents.[18]

Radioprotective & Cytoprotective

The administration of Terminalia chebula (80 mg/kg body weight, i.p.) prior to whole-body irradiation of mice (4 Gy) resulted in a reduction of peroxidation of membrane lipids in the mice liver as well as a decrease in radiation-induced damage to DNA, as assayed by single-cell gel electrophoresis

(comet assay). Terminalia chebula also protected the human lymphocytes from undergoing the gamma radiation-induced damage to DNA exposed in vitro to 2 Gy gamma-radiation. These results suggest the radioprotective ability of Terminalia chebula.[19]

Wound Healing:

Topical application of an alcoholic extract of Terminalia chebula leaves on rat dermal wounds showed that wounds treated with Terminalia chebula healed faster, as indicated by improved contraction rates and a shorter epithelialization period. Reduced lipid peroxide levels in the treated wounds, along with ESR measurement of antioxidant activity through DPPH radical quenching, suggested that T. chebula has antioxidant properties.[20]

Antimicrobial Action:

The herb exhibits antibacterial, antifungal, and antiviral properties, further protecting the body from various infections and enhancing the immune system's effectiveness.

Chondroprotective Effect (Protection of Cartilage):

Protecting the joint cartilage and bone from the degenerative damage characteristic of the disease. A standardized ethanol extract of Terminalia chebula, in a collagen-induced arthritis study, revealed that these benefits were driven by a precise biochemical mechanism: the extract substantially downregulated the production of key pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. Given its efficacy in both reducing inflammation and alleviating pain, coupled with a favorable safety profile, the study concluded that the extract is an up-and-coming natural candidate for the management of Rheumatoid arthritis.[21]

Antiulcerogenic Activity:

Animals pretreated with doses of 200 and 500 mg/kg hydroalcoholic extract showed significant reduction in lesion index, total affected area and percentage of lesion in comparison with control group in the aspirin, ethanol and cold restraint stress-induced ulcer models. Similarly, extracts increased mucus production in aspirin and ethanol-induced ulcer models. At doses of 200 and 500 mg/kg of T. chebula extract showed antisecretory activity in pylorus-ligated model, which led to a reduction in the gastric juice volume, free acidity, total acidity, and significantly increased gastric pH. Hydroalcoholic extract of the fruit T. chebula displays potential antiulcerogenic activity.[22]

Phytochemicals:

Anthraquinone glycoside, tannin, chebulagic acid, chebulic acid, chebupentol, chebulanin, corilagin, neochebulinic acid, ellagic acid, gallic

acid (1.21%), tannic acid, punicalagin, quercetin, arjunolic acid, sennoside A, succinic acid, β-sitosterol, vitamin C, and proteins. The fruit kernel has arachidic, behenic, linoleic, oleic, palmitic, and stearic acid. The flowers contain chebulin and the leaves have terflavins B, C, and D, punicalagin, and punicalatin.[23]

Gallic Acid

Gallic acid impacts immunity by having anti-inflammatory and immunomodulatory effect, suppressing pro-inflammatory cytokines like TNF-α and IL-6, and its antioxidant properties increase the activity of antioxidant enzymes and decrease lipid peroxidation in ovaries and normalize the serum level of sex hormones in PCOS rats. It has been investigated on the serum level of pituitary-ovary axis hormones and action on ovary tissue antioxidant enzymes of PCOS. In animal experimentation with female Wistar rats, GA was given for 21 days orally, and it resulted in levels of LH, estradiol, and testosterone, as well as the MDA in treatment group with GA, which were increased significantly compared to the PCOS group ($p < 0.05$), while the serum level of FSH and progesterone and tissue level of SOD and CAT enzymes were increased significantly in GA-treated groups than the PCOS group.[24]

Chebulic Acid

The study with aqueous extract of Terminalia chebula fruits, which was already proven as antidiabetic effect, has investigated the protective mechanism of chebulic acid isolated from Terminalia chebula, showing significant effect against the progression of AGE-induced endothelial cell dysfunction, suggesting that this compound may constitute a promising intervention agent against diabetic vascular complications.[25]

Chebulagic Acid

It was confirmed that the 80% ethanol extract had a greater content of chebulagic acid from the fruit of Terminalia chebula. It has been compared with rat intestinal α-glucosidase inhibitory activity, and results showed that this drug can control blood glucose and manage type 2 diabetes, which is a causative factor for PCOS.[26]

Hydrolysable Tannin

The analysis of the therapeutic potential of hydrolysable tannin in adult female rats had shown the best therapeutic potential for weight management, reduction of oxidative stress, and improvement in reproductive health of PCOS rats.[27]

Immunomodulator Effect of Harītakī

1. The results obtained in the current study show that Terminalia chebula extract displays a dose-dependent immunostimulatory effect to

antigenic stimulation. Injecting mice i.p. with 10^9 SRBCs suspended in saline sensitizes them for elicitation of DTH and also induces antibody formation; therefore, this system has a major advantage: it enables two components of immune response to be measured in the same species under ideal conditions and is relatively simple and inexpensive to perform. Terminalia chebula extract produced a dose-dependent increase in both the parameters (i.e., antibody production and delayed-type hypersensitivity). Therefore, it is concluded that the aqueous extract of fruit of Terminalia chebula has promising immunostimulant properties.[28]

2. The standardized water extract from Terminalia chebula fruit shows robust antioxidative activity, attributable to its rich polyphenolic composition—including gallic and protocatechuic acids. Though less potent in chemical assays than purified gallic acid, it exhibits superior performance in cellular ROS suppression, highlighting its promise for combating oxidative stress in biological contexts. Moreover, 4 mg of T. chebula extract significantly decreased the incidence, volume, and number of tumors in DMBA/TPA-induced skin tumorigenesis in mice.[29]
3. This study confirms the immunomodulatory activity of ripe T. chebula fruits as evidenced by increase in the concentration of antioxidant enzymes, GSH, T and B cells, the proliferation of which play important roles in immunity. This phenomenon also enhances the concentration of melatonin in the pineal gland as well as the levels of cytokines, such as IL-2, IL-10, and TNF-α, which play essential roles in immunity.[30]
4. In this study, the same extract was evaluated for its immunomodulatory activity against S. typhimurium in vivo. Animals pretreated with the same extract at a dose of 500 mg/kg body wt orally showed an increase in WBC count by 3×10^3/cu mm and lymphocyte count by 4% as compared to saline-treated control challenged with 50,000 colony-forming units of S. typhimurium. The drug showed proliferation of lymphocytes by 102% and increase in food pad thickness by 28.87% as compared to infected control in delayed-type hypersensitivity test. Thus, the

drug showed its protective effect through its immunomodulatory activity in mice and can be used in typhoid.[31]

5. The anti-amoebic effect of a crude drug formulation of T. chebula was investigated in experimental caecal amoebiasis in rats with a curative rate of 89% at 500 mg/kg body weight due to varying degrees of inhibition of enzyme activities such as DNase, RNase, aldolase, alkaline phosphatase, acid phosphatase, α-amylase, and protease in axenically cultured amoebae.[32]
6. It is mainly used as an astringent, laxative, stomachic, and tonic. T. chebula has been investigated for its effect on cell-mediated and humoral components of the immune system.[33]
7. Crude extract of T. chebula stimulated cell-mediated immune response in experimental amoebic liver abscess in golden hamsters.[34]
8. Aqueous extract of T. chebula produced an increase in humoral antibody titer and delayed-type hypersensitivity in mice.[35]

Discussion

Terminalia chebula, commonly known as Harītakī, occupies a prominent position in Ayurvedic medicine due to its extensive therapeutic properties. This study consolidates evidence from diverse pharmacological investigations to elucidate Harītakī's immunomodulatory effects. The herb's role as a Rasāyana, aimed at promoting longevity and vitality, is underscored by its ability to enhance immunity through various mechanisms.

Harītakī's immunostimulatory action is supported by studies demonstrating its capacity to boost both cellular and humoral immune responses. For instance, research has shown that Harītakī extract promotes lymphocyte proliferation and increases the production of key cytokines such as IL-2, IL-10, and TNF-α, crucial for immune function regulation. These effects suggest that Harītakī could potentially enhance host defence mechanisms against infections and diseases.

Moreover, Harītakī exhibits antioxidant properties, as evidenced by its ability to elevate levels of glutathione (GSH) and antioxidant enzymes. This antioxidative capacity is vital in mitigating oxidative stress, a contributing factor to various chronic ailments and aging processes.

The herb's therapeutic potential extends beyond immunomodulation to encompass other health benefits. Studies highlight Harītakī's efficacy in managing conditions such as diabetes and amoebiasis. Its antidiabetic properties,

attributed to compounds like chebulic acid, indicate promise in regulating blood glucose levels and preventing diabetic complications. Similarly, Harītakī's anti-amoebic activity has been demonstrated in experimental models, suggesting its utility in treating parasitic infections.

The findings from this review underscore the holistic approach of Ayurveda in leveraging natural substances like Harītakī to promote health and well-being. However, further clinical studies are warranted to validate these findings and explore Harītakī's potential as an adjunct therapy in modern medical practices. Overall, Harītakī emerges as a potent immunostimulant with broad therapeutic applications, deserving further investigation for its role in enhancing immune function and overall health promotion.

Limitations & Future Directions

- Most evidence comes from in vitro and animal studies; clinical trials evaluating isolated Harītakī extract are limited.
- Active ingredients and optimal formulations (extracts vs whole fruit vs polyherbal mixtures) need standardization and validation.
- Future studies should compare the effects of Harītakī and modern immunomodulators in clinical trials, focusing on long-term immune system health and recovery, and across different age groups or disease states.

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