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IMMUNOMODULATORY EFFECTS OF HARITAKI (TERMINLIA CHEBULA RETZ.): A REVIEW

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ABSTRACT

A tremendous increase in the knowledge of herbal drug constituents, their effects and side effect has occurred in recent years. Alteration in the immune system can be achieved by immunomodulatory agents from plant source, low molecular weight compounds like Alkaloids and other nitrogen containing compounds, Terpenes, Phenols and high molecular weight compounds like Lectins, Polysaccharides. Herbal medicines constitute a major component in all traditional and alternative systems of medicines like Siddha, Ayurveda, Homeopathy, Naturopathy. The present review immunomodulatory effects of *Terminlia chebula* with immunomodulation action and also to provide insights into the future research in this area.

KEYWORDS: Immunomodulatory, immunomodulation, *Haritaki.*

INTRODUCTION

Plants and other natural products have been in use for ages for health and maintenance of life. The Vedic literature, the most authentic, ancient Indian scripture, gives the reference of many plants for different diseases and their prevention. Rig and Sama Veda describes 67 plants, Yajour Veda 81, Atharva Veda 289, Brahamana 129, while in Upanishads 31 plants are referred.[1] A significant part of Ayurvedic therapeutics aims at prevention of disease. This is the concept of '*Vyadhirodhak Chamatav*' i.e. capacity of the body to resist disease.[2] The Ayurvedic system of medicines not only provides that alternative, but also scores over the side effects and cost factor of allopathic medicine. Immunomodulation is the process that alters the immune system of the host resulting in either immunostimulation or immunosuppression thus regulating or normalizing it. Hence, immunomodulators referred to

as biological response modifiers, improve the host defense mechanism against diseases by striking a balance between regulatory and effector cells.[3,4]

AIMS AND OBJECTIVE

To study the immunomodulatory effects of *Haritaki*(terminlia chebula retz.)

MATERIALS

Different articles, journal and books were analyzed and reviewed for literature about *Haritaki* (terminlia chebula retz.) and its immunomodulatory effect.

LITERATURE

Immune System

The basic function of immune system is to detect and destroy the non-self and thus a defense mechanism. The system works throughout the body through an intricate regulation of cellular and humoral factors. Its protective task, starting with the recognition of non-self bodies and substances puts the immune system in a vital position between a healthy and diseased state of the host. 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 tumors 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 morespecifically interleukins.[5]

Disorders of human immunity: The immune system is a remarkably effective structure that incorporates specificity, inducibility and adaptation. Failures of host defense do occur, however, and fall into three broad categories: immunodeficiencies, autoimmunity, and hypersensitivities.[6]

Immunodeficiencies

Immunodeficiencies occur when one or more of the components of the immune system are inactive. However, malnutrition is the most common cause of immunodeficiency in developing countries. Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocyte function, Ig A antibody concentrations, and cytokine production. Deficiency of single nutrients such as zinc; selenium; iron; copper;

vitamins A, C, E, and B6; and folic acid (vitamin B9) also reduces immune responses. Immunodeficiency's can be inherited or 'acquired'.[6]

Autoimmunity

Autoimmune disease arises when the body mounts an immune response against itself due to failure to distinguish self tissues and cells from foreign antigens. Examples of such diseases include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and insulin-dependent diabetes mellitus (Type 1diabetes).[7,8]

Hypersensitivity

Hypersensitivity can be classified as antibody-mediated or cell-mediated. Three types of hypersensitivity are antibody-mediated (types I-III), while the fourth is cell-mediated (type IV). Hypersensitivity occurs in two phases: the sensitization phase and the effectors phase. Sensitization occurs upon initial encounter with an antigen; the effectors phase involves immunologic memory and results in tissue pathology upon a subsequent encounter with that antigen.[9]

Drugs That Modify The Immune Response

Immunomodulatory drugs are Disease Modifying Drugs (DMDs).

1) Immunostimulants[10]	Synthetic compounds E.g. Isonosine, Levamisole. Immune globulin Cytokines E.g. interferon (INF-α), Interleukins (IL-2) Peptides E.g. dialyzable leukocyte extracts, neuropeptides, thymic factors. Microorganisms E.g. Basillus Calmette-Guerin (BCG), Muramyl dipeptides, Streptococcal components, Nocardia Components, pseudomonas components and Salmonella components.
2) Immunosuppressant[11]	Specific T- cell inhibitors (calcineurin inhibitors) E.g. cyclosporine, tacrolimus Cytotoxic drugs (Antiproliferative drugs) E.g. Azathioprine, Cyclophosphamide, methotraxate, chlorambucil, mycophenolatemofetil. Glucocortcoids E.g. Prednisolone and others. Antibodies. E.g. Muromonal CD3, antithymocyteglobulin, Rho (D) immunoglobulin
3) Immunoadjuvant[12]	The immunoadjuvant hold the promise of being the true modulators of immune response. It has proposed to exploit them for selecting between cellular and humoral, Th1 (helper T1 cells) and Th2, (helper T2 cells) immunoprotective and immunodestructive, and reagenic (IgE) versus immunoglobin G (IgG) type of immune responses, which poses to be a real challenge to vaccine designers.

Haritaki (Terminalia chebula Retz.)

Haritaki is having great value in Ayurveda for its properties in and curing disease. It is always listed first in Ayurveda classics because of its extraordinary therapeutic benefits. They are reported to contain tannins (30-40%) e.g. chebulinic acid, neochebulinic acid, corilagin, chebulagic acid, gallic acid, ellagic acid, punicalagin, terchebin and terflavin A. They also have flavonoids e.g. luteolin, rutins and quercetin in them. Apart from these, they also contain other phytochemicals such as anthraquinones, saponins, β-D-glucogallin, 1, 3, 6-trigalloyl glucose, 1, 2, 3, 4, 6-penta-O-galloyl and various other carbohydrates, amino acids and fatty acids.

Botanical classification: According to Benthem & Hooker (1862-1883)

Taxonomical position : *Terminlia chebula* Retz.	Order : Myrtales
Kingdom : Plantae	Family : Combretaceae
Division : Magnoliophyta	Genus : Terminalia
Class : Magnoliopsida	Species : chebula Retz.

Vernacular Names

Assami: Hilikha, Bengali: Haritaki, Burma: Pangah, English: Black myrobalan, chebulic myrobalan, Gujarati: Hirdo, Harade., Hindi: Har, Harara, Harra., Konkani: Ordo Malayalam: Divya, Katukka, Kayastha, Putanam, Punjabi: Halela, Har, Harrar, Hurh Tamil: Amagola, Telugu: Haritaki, Karaka, Karakkaya, Nallakaraka, Resaki, Sringitiga Tulu: Anile, Urdu: Haejarad, Uriya: Horida, Horitoki, Jonghihorida, Karedha.

Botanical Description[13]

Habitat**:** It is found throughout the greater parts of India, from Ravi eastwards to West Bengal and Assam, ascending to an altitude of 1500 m in the Himalayas, also in Bihar, Orissa, Madhya Pradesh, Maharashtra, Deccan and South India. Habit**:** A moderate sized or large deciduous tree, attaining 15-24 meters in height. Fruit**:** Drupes ellipsoidal, obovoid or ovoid, yellow to orange brown, and hard when ripe, 3-5cm long, 5 ribbed on drying.	Leaves**:** Ovate or elliptic with a pair of large glands at the top of the petiole. Flowers**:** Flowers all hermaphrodite, 4mm. Across sessile, dull-white or yellow, with an offensives small. Spikes-sometimes simple, usually in short panicles, terminal and in the axils of the uppermost leaves. Seeds**:** Hard, pale yellow. Flowering and fruiting time-Rains to summer season.

Synonyms[14]

Abhaya, Pathya, Kaystha, Putna, Amrita, Hemvati, Avyatha, Chetaki, Shreyasi, Shiva, Vayastha, Vijaya, Jivanti, Rohini.

Types [15]

According to *Bhavprakash Nighantu*, it is of 7 types viz. *Vijaya, Rohini, Putna, Amrita, Abhaya, Jivanti and Chetaki. Chetaki* is further of 2 types *Shukla* (of 6*angula*) and *Krishna* (1 *angula*). The best among the 7 is *Vijaya*.

Pharmacodynamics[16]

Rasa (Taste)- *Panch rasa (except lavana* i.e. salt*)*

Guna (Property)- *Laghu* (light), *Ruksha* (Dry)

Virya (Potency)- *Ushna* (Hot)

Vipaka (Metabolism)- *Madhur* (Sweet)

Effect on *Tridosha*[16]

Being *Madhura* (sweet), *Tikta* (Bitter) and *Kashaya* (Astringent) in rasa it harmonizes *Pitta*.

By its *Katu* (Pungent), *Tikta* (Bitter) and *Kashaya* (Astringent) rasa it harmonizes *Kapha*.

By its *Amla* (sour) and *Madhura* (Sweet) *rasa* it balances *Vata*.

Thus it is *Tridoshhar* but predominantly *Vatashamak* (subsides aggravated *Vata*).

Formulations[17]

Abhayamodaka, Abhyarisht, Pathyadichurna, Pathyadivati, Pathyadikwatha, Vyaghri Haritaki, Agastya Haritaki, Chitrak Haritaki, Danti Haritaki, Dshmula Haritaki, Triphlachurna, Phaltrikadikwatha, Bramharasayna, Haritakikhanda.

Phytochemical Constituents of *T. Chebula* Retz

The plant is found to contain phloroglucinol and pyrogallol, along with phenolic acids such as ferulic, p- coumaric, caffeic and vanillic acids. Some of the other minor constituents were polyphenols such as corilagin, galloyl glucose, punicalagin, terflavin A, maslinic acid.[18]

Besides, fructose, amino acids, succinic acid, beta sitosterol, resin and purgative principle of anthraquinone are also present.[19,20]

Flavonol, glycosides, triterpenoids, coumarin conjugated with gallic acids called chebulin as well as other phenolic compounds were also isolated.[21,18,22,23]

Twelve fatty acids were isolated from *T.chebula* of which palmitic acid, linoleic acid and oleic acid were main constituents.[24]

Triterpenoid glycosides such as chebulosides I and II, arjunin, arjunglucoside, 2α-hydroxyursolic acid and 2α-hydroxymicromiric acid also have were reported.[25]

Oil extracted from kernels yielded palmitic, stearic, oleic, linoleic, behenic and arachidic acids.[26]

The fruits of *T. chebula* are rich **in tannins (about 32%-34%)** and its content varies with geographical distribution.[27,28]

The tannins of *T. chebula* are of pyrogallol (hydrolysable) type. A group of researchers found 14 components of hydrolysable tannins (gallic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid,ellagic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl- β-D-glucose, 1,6-di-ogalloyl-D-glucose, casuarinin,3,4,6-tri-oglloyl-D-glucose, terchebulin) from *T.chebula* fruits.[28]

Other constituents include phenolics such as chebulinic acid, ellagic acid and anthraquinones. The leaves were found to contain polyphenols such as punicalin, punicalagin, terflavins B, C and D.[29-31]

Immunomodulatory activity

The initial study on aqueous extract of *T. chebula* for its immunomodulatory activities has been reported. The study was based on assessment of humoral antibody titre and delayed type hypersensitivity (DTH) test.[32] A detailed study on immunomodulatory activity of its aqueous extract has also been reported, where the model animals were pretreated with 500 mg/kg of extract orally and challenged with 50 000 CFU of *S. typhimurium*. The animals showed $3\times10^3/mm^3$ increase in WBC count and 4% increase in lymphocyte count as compared to saline treated control animals. It was also reported that there was 102% increase in lymphocyte proliferation and 28.87% increase in foot pad thickness as compared to the infected control in DTH test. Thus the study concluded that the extract shows its protective effect through its immunomodulatory activity in mice against typhoid.[33] The aqueous extract reportedly increased humoral antibody titer[34] and therefore, it can be concluded that killing of *S. typhimurium* takes place via humoral response too.

The biologically active compounds such as chebulagic acid, gallic acid and ellagic acid make *T. chebula* highly potent antioxidant, which may be responsible for its immunomodulatory activity.[35,36,37]

Its extract neutralizes reactive oxygen species (ROS) and scavenges free radicals. The free radicals are responsible for causing inflammation by stimulating release of cytokines such as IL-1, TNF-α and IFN-β, which stimulate additional neutrophils and macrophages at site of inflammation.[38] Thus, different antioxidants of the extract exhibit immunosuppressive properties, which help in neutralizing these important inflammatory mediators. Thus, different antioxidants of the extract exhibit immunosuppressive properties, which help in neutralizing these important inflammatory mediators.

Another study was conducted on the alcoholic extract of *T. chebula* focusing on its immunomodulatory activity.[39] The results indicated elevated levels of different antioxidant enzymes, glutathione and T- and B-cells suggesting its role in immunostimulation. Further the study reported increase in concentration of melatonin in pineal glands as well as the cytokines such as IL-2, IL-10 and TNF-α which play crucial role in immunity, thereby focusing on its immunostimulant property.

DISCUSSION

Immunomodulation using medicinal plants can provide an alternative to conventional chemotherapy for a variety of diseases especially when host defense mechanism has to be acquired under the conditions of impaired immune responsiveness.[40] Indian medicinal plants are a rich source of substances which are claimed to induce paraimmunity, the non-specific immunomodulation of especially granulocytes, macro-pages, natural killer cells and competent functions. Immunostimulation and immunosuppression both need to be tackled in order to regulate the normal immunological functioning.

CONCLUSION

Use of traditional medicines for improving immunity and treating various diseases has been approved by WHO. India has a rich documented history of traditional medicines such as *Sushrut Samhita* and *Charak Samhita*. Presently for treating various ailments allopathic drugs are preferred, which are not only very expensive but pose a great threat by causing mild to severe side effects. None of these problems occur with the prescribed dosage of plant-based medicines.

To shift the focus from conventional allopathic drugs to traditional plant based drugs a more comprehensive and focused study is required targeting molecular level by isolating, identifying and conducting phase-wise clinical trials of active compounds. This would not only help in generating awareness and greater acceptance amongst physicians but also among general public.

In this regard, this review is a step towards evaluating the pharmacological properties of *Haritaki*. The review indicates presence of different active compounds in them such as gallic acid, chebulagic acid, ellagic acid, flavonoids, tannins and phenols, which are responsible for its effective immunostimulatory and immunosuppressant property making it a strong contender as a plant based Ayurvedic immunomodulator.

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