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Immunomodulatory Effects of *Triphala* and its Individual Constituents: A Review

Pranoti Belapurkar,* Pragya Goyal, and Preeti Tiwari-Barua

Department of Biotechnology, IPS Academy, Rajendra Nagar, AB Road, Indore-452 012, India
***Address for correspondence** E-mail: pranotivivek@gmail.com

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Abstract

Go to:

The role of plant extracts and Ayurvedic polyherbal preparations in treating various ailments has been acknowledged since time immemorial. Studies based on the effect of these extracts in treatment of different diseases have also been well documented. Indian medicinal literature also emphasizes the synergistic effect of polyherbal drugs in restoring and rejuvenating immune system. This review focuses on the immunomodulatory potential of the polyherbal preparation, *Triphala* and its three constituents, *Terminalia bellerica*, *Terminalia chebula* and *Emblica officinalis*. The role of *Triphala* and its extract has been emphasized in stimulating neutrophil function. Under stress condition such as noise, *Triphala* significantly prevents elevation of IL-4 levels as well as corrects decreased IL-2 and IFN-γ levels. Under the condition of inflammatory stress its immunosuppressive activity is attributed to its inhibitory action on complement system, humoral immunity, cell mediated immunity and mitogen-induced T-lymphocyte proliferation. The aqueous and alcoholic extracts of the individual constituents reportedly enhance especially the macrophage activation due to their free radical scavenging activity and the ability to neutralize reactive oxygen species. This study thus concludes the use of *Triphala* and its three individual constituents as potential immunostimulants and/or immunosuppressants further suggests them to be a better alternative for allopathic immunomodulators.

Keywords: *Triphala*, *Terminalia bellerica*, *Terminalia chebula*, *Emblica officinalis*, Immunomodulator

Ayurveda, the oldest healing science, focuses on treating different ailments through balancing the three pillars of life, *vat*, *pitta* and *kaf*. The role of different plant extracts in maintaining this balance and also treating various diseases is also well documented. However, in recent past in-depth research is focusing more on the phytochemical analysis of these extracts and their effects on various disease conditions *in vitro*. These plant extracts have proven to be important for reestablishing body's equilibrium and providing resistance against infection. They also possess the restorative and rejuvenating powers as they act on the immune system and positively affect the response of the body towards infection[1].

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[2,3]. Using this quality of biological mediators, various alternative Ayurvedic formulations have been developed for various diseases where they either activate the host defense mechanism e.g. in case of impaired immune response or can selectively suppress it in conditions like autoimmune disorders and hypersensitivity. Such

immunomodulatory properties of various medicinal plants provide an alternative to conventional synthetic drug therapy, which causes side effects, allergic reactions, tolerance to drugs and increased resistance of microorganisms to antibiotics.

The active components of various medicinal plants regulate the immune system by interacting with various immunocytes and regulating their effector mechanism for instance, cytokines and their receptors. These active components, referred to as *rasayanas* in Ayurveda, in sync with balanced diet impart vigor and longevity to individuals. This is called as *rasayana* therapy. Apart from this these active components play crucial role in enhancing body's resistance towards various diseases, memory and energy, which ultimately balances the health of the individual as a whole.

One of the important *rasayanas* in Ayurveda is *Triphala*, a polyherbal *tridoshic rasayana* consisting of *Terminalia bellerica Roxb*. (Family Combretaceae), *Terminalia chebula Retz*. (Family Combretaceae) and *Emblica officinalis* (Family Euphorbiaceae) in equal proportions. The present article aims at highlighting the immunomodulatory properties of the Ayurvedic *rasayana Triphala* and its three different constituents. It further focuses on generating awareness and acceptance of such Ayurvedic formulations in the society.

TERMINALIA CHEBULA RETZ.

Go to:

Geographical distribution, phytochemistry and therapeutic uses:

T. chebula Retz. belongs to family Combretaceae and is found abundantly in different states of India like Madhya Pradesh, Gujarat, Maharashtra, Tamil Nadu, Karnataka and Bengal[4]. It is commonly called as Chebulic Myrobalan in English, *Harad* or *Harra* in Hindi and *Abhaya* in Sanskrit[5,6,7]. The tree is deciduous whose fruits are drupes with longitudinal wrinkles and a fibrous pericarp. They are oval to ellipsoid, 2-4 cm long and 1.5-2.5 cm broad. They are reported to contain tannins (30-40%) e.g. chebulinic acid[8], neochebulinic acid, corilagin, chebulagic acid[9,10], gallic acid, ellagic acid, punicalagin, terchebin and terflavin A. They also have flavonoids e.g. luteolin, rutins and quercetin in them[11]. 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[12,13,14,15,16,17].

Due to presence of range of biologically active compounds, the fruits of *T. chebula* have been used in traditional medicine to combat a number of ailments of upper respiratory tract, gastrointestinal tract, urinary tract and skin[15,18,19,20,21,22,23,24]. These active compounds are effective in treating cancer[15] and other diseases of the heart, nervous system, bones and joints. Reportedly, the active components of the fruit have an antiageing effect, thus increasing the life span of the individual[11].

It has been reported to be an effective antibacterial agent against a wide range of Gram-positive and Gram-negative bacteria[25,26,27,28], antifungal agent against various pathogenic fungi[28,29,30,31] and an antiviral agent against swine influenza A virus, HSV-1, HIV-1 and cytomegalovirus[32,33,34]. The studies conducted have also inferred that the fruits of *T. chebula* act strongly against HBS antigen, inhibit HBV DNA polymerase and also significantly increased IFN-γ and IL-2 levels in peripheral blood mononuclear cell culture, thus emphasizing its antiHBV activity[35]. Further the studies have indicated it to be used as an antioxidant[36,37], antiinflammatory, antianaphylactic, antimutagenic[38,39], antinociceptive[40] and in wound healing activities[41,42].

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[43]. 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[44]. The aqueous extract reportedly increased humoral antibody titer[43] 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[24,45,46]. 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[47]. 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[48]. 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.

TERMINALIA BELLERICA ROXB.

Go to:

Geographical distribution, phytochemistry and therapeutic uses:

T. bellerica Roxb. also belongs to family Combretaceae and apart from dry and desert regions of India, it occurs commonly in mixed deciduous forests of Punjab, Haryana, Uttar Pradesh, Madhya Pradesh and Maharashtra[5,7,16,49,50]. It has various names i.e. Beleric Myrobalan in English, *Baheda* in Hindi and *Bibhitaki* in Sanskrit[51]. The fruits of *T. bellerica* Roxb. are ovoid drupes, 2-3 cm long and 1-2 cm in diameter, grey to dark brown in colour, 5 distinct ridges present externally, densely covered with hair and velvet to touch. Fruits narrow into a very short stalk which on drying leaves a very prominent scar at the base[6,52,53]. The fruits are reported to contain gallotannic acid, ellagic acid, gallic acid, lignins such as termilignin and thannilignin and anolignan-B[54], 7-hydroxy-3, 4-flavone, ethyl gallate, galloyl glucose, chebulaginic acid, phenyllemblin, β-sitosterol, anthraquinones, glycosides such as bellaricanin[54,55] and other carbohydrates[51,54,56]. The oil content of the fruit is high (30-40%) as it contains palmitic, stearic, oleic and linoleic acid[15,16]. The fruit extract is reported to be acrid, astringent, antioxidant, antipyretic, antiemetic, antiinflammatory, anthelmintic, antidiabetic, antidiarrhoeal and analgesic[57,58,59,60,61,62]. It is also a good brain tonic, expectorant and laxative; used as a blood purifier and a rejuvenating drug[63,64,65]. The fruit extract possesses high antimicrobial activity specifically against Gram-positive bacteria[28,66] e.g. *B. subtilis* and *S. aureus*, pathogenic bacteria and yeasts and moulds e.g. *C. albicans* and *A. niger*[28]. However, it is shown to decrease pathogenicity of Gram-negative motile bacteria e.g. *S. typhi*, *S. typhimurium*, *E. coli* and *P. aeruginosa* by rendering them less motile[66].

Immunomodulatory activity:

Lately, the focus of the work is on assessing the immunomodulatory effect of *T. bellerica* extract. Since different activities of the extract have been attributed to the various biologically active compounds present in it, it is likely that some of these influence the host immune system as well. Gallic acid of many different plant extracts has been reportedly responsible for increasing ROS production in macrophages resulting in their increased phagocytic activity[67,68,69]. *T. bellerica* fruit extract is also rich in gallic acid content and therefore has been reported to be responsible for increasing the phagocytic activity of macrophages. The other mechanism for the enhanced phagocytic activity of the extract is due to some alteration in the mechanism of action of related enzyme such as phosphotyrosine phosphatase resulting in superoxide anion production[70]. This property of the extract makes it a

potential drug against microbial infection and cancer[71]. Another study performed on mouse models reported the methanol extract of *T. bellerica* to be a potent stimulus for enhanced T-lymphocyte proliferation as compared to phytohaemagluttinin (PHA) alone. When the extract was administered with lipopolysaccharides (LPS) and poke weed mitogen (PWM), T-cell-independent B-cell proliferation was more enhanced indicating better cell-mediated immunity (CMI) than humoral-mediated immunity (HMI) and also reported to induce mouse spleenic B-cell through T-cell independent mechanism. Therefore, the study concluded that gallic acid from different plant extracts is the active component responsible for stimulation of immune system of mice[72]. These results were later confirmed by another study[73].

EMBLICA OFFICINALIS LINN.

Go to:

Geographical distribution, phytochemistry and therapeutic uses:

Emblica officinalis Linn. (Family Euphorbiaceae) is indigenous to mixed deciduous forests of tropical India. In English it is called as Embelic Myrobalan or Indian Gooseberry, in Hindi it is called as Amla and in Sanskrit it is mentioned as *Amlaki* or *Amlakan*[5]. Fruits are pale green, globose, fleshy and 6-lobed with 3 segments. They are 1.5-2.5 cm in diameter and its mesocarp is edible and the endocarp is stony[49,52,74]. On ripening they are extremely acidic, astringent with distinct bitter flavor. They are also cooling and refrigerant in nature[75].

It is reported to contain phenolic constituents like gallic acid and its derivatives, mucic acid and its derivatives, corillagin, chebulagic acid, putrajivain A[76,77]. They possess high amounts of tannins like emblicanin A and B, punigluconin and pedunculagin[78], flavonoids like quercetin[79,80] and alkaloids like phyllantin and phyllantidin[81]. Various groups have reported high amounts of vitamin C[82,83,84,85,86] and considerably high amounts of minerals, proteins and amino acids like proline, alanine, cysteine, glutamic acid, aspartic acid and lysine. The fruits also contain glucose, fibers, phosphorus, iron and calcium[12,87].

The fruit is highly beneficial as cytoprotective[88], hepatoprotective[89,90], radioprotective[91], gastroprotective[92] and antitussive agent[93]. It is used to treat ophthalmic disorders, diarrhea, diabetes, scurvy, tumor, and ulcer[92,94,95,96,97,98,99,100,101,102] and protects against hyperthyroidism[103], cataract[100], ischemic reperfusion induced oxidative stress[104,105], atherosclerosis and hyperlipidemia[106,107,108,109]. It is also a potent antibacterial agent against Gram-positive and Gram-negative bacteria[28,110,111,112] as well as an antifungal agent[28,111].

Immunomodulatory activity:

Various studies have proved the fruit extract to be strongly immunomodulatory when Cr (VI) was used as immunosuppressant drug. It possesses antiapoptotic property and ceases DNA fragmentation, thus countering the immunosuppressive effect of Cr (VI) on lymphocyte proliferation. Further, it considerably restores IL-2 and IFN-γ production. This helped in restoring antioxidant status against Cr (VI) induced free radical production back to control level[113,114].

In another study, the immunomodulatory activity of aqueous extract of *E. officinalis* was reported. It showed that *E. officinalis*-treated mice had significantly higher antisheep RBC titer and DTH reaction compared to the control. This was concluded because of significant increase in WBC count and % lymphocyte distribution in *E. officinalis*-treated mice, suggesting its ability to stimulate haemolymphopoetic system[115]. *E. officinalis*-treated groups also produced high serum protein especially serum globulin and the mice also showed increase in spleen weight suggesting increased immunocompetence in them[116]. All these results indicated stimulant effect of *E. officinalis* on both CMI and HMI responses. Further the studies concluded that the extract caused significant increase in migration area as well as nitro blue tetrazolium (NBT) reduction of peritoneal macrophages in *E. officinalis*-treated mice as compared to control group indicating the role of extract in macrophage activation. This was accompanied by burst of oxidative metabolism generating ROS detected through NBT assay, confirmed the intracellular killing

property of phagocytosing macrophages[115].

TRIPHALA

Go to:

Triphala as mentioned earlier is made of equal amounts of dried fruits of *T. chebula*, *T. bellerica* and *E. officinalis*. Thus the phytochemicals present in it are those of its individual components, making it rich in gallic acid, tannins, chebulagic acid, ellagic acid, phenols and glycosides[117].

In Ayurvedic literature, *Triphala* is mentioned as a bowel regulator, tonic, cleanser, blood purifier and as an eyewash to counter many eye ailments e.g. conjunctivitis and to remove redness and soreness of eyes. It is also used to alleviate headache, dyspepsia, constipation, liver conditions and leucorrhoea. It is reported to be an effective antibacterial agent against Gram-positive and Gram-negative bacteria, antifungal agent[28], antidiabetic[68], radioprotective[118], antimutagenic[39], antioxidant[119,120], chemopreventive agent[121,122,123], analgesic, antipyretic[124,125,126], anticancer[15,123,127] and hypolipidaemic agent[128]. It is also reported to work against dental caries[129].

Immunomodulatory activity:

Triphala as a whole has been reported to be good for health and is used for its therapeutic actions. Recent extensive research has regarded it to be an extraordinary preparation with huge benefits such as adaptogenic and immunomodulation. A study was conducted to assay the immunomodulatory activity of *Triphala* using neutrophil functions like adherence, phagocytosis and NBT reduction in albino rats[130]. The study group of rats was exposed to noise stress of 100dB for 4 h/day for 15 days and their neutrophil function tests and corticosterone levels were assessed. The group that was administered *Triphala* 1 g/kg/day for 48 days showed significantly enhanced avidity index with no change in neutrophil function and steroid levels. The *Triphala* administered group, immunized with sheep RBC (5×10^9 cells/ml), showed significant decrease in corticosterone levels. The groups viz. noise stress and noise stress immunized groups showed significantly suppressed neutrophil function, followed by significant increase in corticosterone levels. The study showed that administration of *Triphala* in both groups i.e. noise stress alone and noise stress immunized group greatly prevented the effect of noise stress, which was evident by its immunostimulant effect on neutrophil function and immunosuppressant effect on corticosterone levels of the model animals. Another study was conducted to evaluate the immunomodulatory effect of *Triphala* based on the analysis of the antibody titre, Pan-T, CD^{4+}/CD^{8+} lymphocyte phenotype in spleen and different cytokines like IL-2, IL-4 and IFN-γ[131]. Four groups of rats were employed namely, control, *Triphala* (1g/kg), noise stress (100dB for 4 h/day for 15 days), *Triphala*+noise stress immunized by sheep RBC (5×10^9 cells/ml). The results showed elevation in serum antibody titre and IL-4 levels accompanied by decreased IL-2, IFN-γ levels and reduction in Pan-T, CD^{4+}/CD^{8+} lymphocyte phenotype in spleen induced by noise stress. However, these effects were significantly prevented in the rats those were exposed to noise stress after being treated by *Triphala*, thus suggesting its therapeutic effectiveness.

Another study evaluated the immunomodulatory effects of *Triphala* powder on experimentally induced inflammation in mice[132]. The investigation was based on assessment of complement activity; HMI and CMI in mice and PHA-induced T-lymphocyte proliferation *in vitro*. The study was conducted on two groups of six mice each, both of which were inoculated with 0.1 ml of complete Freund's adjuvant in right hind paw to induce inflammation. The mice of both groups were orally administered with a dose of 500 mg/kg of *Triphala* powder, 1 h before induction of the adjuvant. The same dose continued for 5 days for one group while the other group was kept as control. *Triphala* administration showed significant inhibition of complement activity, HMI, CMI and mitogen-induced T-lymphocyte proliferation in a dose-dependent manner. These results suggested immunosuppressive activity of *Triphala* in experimentally-induced inflammation indicating its efficacy in treating inflammation and other autoimmune diseases.

The adaptogenic and immunomodulatory activity of *Triphala* megaext was assessed by a group of workers[133].

The megaext was prepared by mixing together six different extracts of *Triphala* made using non- polar to polar solvents (petroleum ether, benzene, chloroform, ethyl acetate, 70% ethanol and water). The extracts were then concentrated by distilling the solvent and air-dried. This megaext reportedly contained alkaloids, carbohydrates, glycosides, terpenoids, protein and amino acids, phenolics and tannins, flavonoids, oils, fats and saponins. The LD_{50} of this extract was determined to be 2000 mg/kg on Swiss albino mice. Five hundred and 1000 mg/kg doses were selected for *in vivo* study. The two parameters studied were carbon clearance assay (CCA) and DTH. The group of mice receiving 500 mg/kg p.o. as well as 1000 mg/kg p.o. showed significant increase in phagocytic index as compared to the control group, which received 25 mg/kg p.o. livomisole as a standard immunomodulator. This increase in carbon clearance index clearly shows enhancement of phagocytic function of mononuclear macrophages and thus non-specific immunity. The megaext thus enhanced the phagocytic function, which was exhibited by the clearance rate of carbon by the cells of reticulo-endothelial system.

In the same two groups DTH was used to study the CMI response of *Triphala* megaext where the foot pad edema was induced in Swiss albino mice and the paw edema value was observed. Increase in paw edema value was indicative of CMI response. There are two phases of DTH response. The first comprises of sensitization phase, which comes after the initial contact with sheep RBC antigen followed by the effector phase that comes after subsequent exposure to sheep RBC antigen. In this latter stage a variety of cytokines are secreted by T_H1 cells that help in recruitment and activation of macrophages and other nonspecific inflammatory mediators. Both the treated groups showed an increase in DTH as compared to the control groups. This clearly indicates the stimulatory effect of megaext on immune cells in response to T-cell-dependent antigen.

CONCLUSION

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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 *Triphala* and its three different constituents. 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.

Footnotes

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Belapurkar, *et al*.: Immunomodulatory Effects of *Triphala*

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