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Review on potential antiviral and immunomodulatory properties of Piper Longum

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Abstract. Piper longum traditionally known as Pippali is a climbing vine belonging to the Piperaceae family, which originated in northeastern India and the Western Ghats. It is majorly used in traditional and Ayurvedic system of medicines to treat bronchitis, diarrhea, viral hepatitis, respiratory infections, stomach pain, bronchitis, spleen diseases, coughs, colds and tumors. Articles indexed by Scopus, electronic search as Science Direct, PubMed, are used to collect information about Piper longum. There are many phytochemicals in Pippali, including alkaloids, essential oils, flavonoids and steroids. The pharmacological properties reveal the anti-inflammatory, antimicrobial, adulticidal, anti-obesity, anti-fungal, antipyretic and cardio protective effects of the plant. Pipili also has many antiviral activities, and helps to improve the immune system and effectively resist hepatitis B virus. This plant seems to be non-toxic, easy to obtain, inexpensive, and has no side effects. Although there are infinite traces for its medicinal use, however its use in treating viral influenza like diseases is not yet much explored. However, it has strong potential to treat symptoms such as cough, cold and fever. In the wake of the current situation of the global corona virus, it has become essential to look for alternatives that would be effective against the virus as well as provide the additional immunity boosting ability. Therefore, effective experimentation and investigations are essential to consider its competence. Researchers must study the plant in details for its huge potentialities.

Key words: Piper longum, hepatitis B virus, immunity boosting

1. Introduction



Since ancient times, the medicinal properties of plants have always been the most important. These plants are well known to local communities and are an integral part of their lives. The plants like capparidaceae DC has antioxidant, antimicrobial and anticancer studies. Piperaceae is one of the important plant families, mainly including herbs, shrubs, vines or trees. The Piperaceae family which includes thousands of species approximately to 4000 and further divided into 5 common genera. Two important genera are Piper which includes about 2000 species and Peperomia includes 1600 species. The members of the Piper genus are mainly traced to tropical regions of the world. Pipers are considered to have economic and medical value, such as bagpipes, flutes, cubes, black pepper, etc. *Piper longum* fruits since ancient times were famous as spice and common ingredient of preservatives in pickles, food items, traditional drinks, medicines. The fruits have a flavor that resembles black pepper and thus adulterated as ground black pepper as it also comparatively less expensive.. In Indian medicinal systems of Ayurveda, Siddha, and Unani, Piper longum is widely used. The part of roots and fruits of *P. longum* plant are used to treat asthma and bronchial distress, hemorrhoid infections, fever, inflammation, abdominal pain, jaundice and antidote to snake bite and the stems are used to relieve postpartum pain, rheumatic pain and diarrhea.. Pippali (*P. longum*) is used to stimulate the digestive system and respiratory system, and has a rejuvenating effect on the lungs. *Piper longum* posses many secondary metabolites some of those are alkaloids, flavonoids, steroids, essential oils, cardiac glycosides, anthraquinones, arbutin, anthraglycosides, etc. The most abundant alkaloid present is piperine. 4-5% of the alkaloid piperine is present which contributes to the unique pungent taste. The previously published reviews provides information on the pharmacological properties of *Piper longum* such as the antitumour, immunomodulatory, antifungal, antimicrobial, anti-inflammatory, anti-obesity, cardioprotective, antioxidant, hepatoprotective, antidepressant, anti-moebic and several other properties. The compounds extracted from Piper species also show significant anticancer properties. Piper longum is also widespread for its role as bioenhancers, which increases the bioavailability, tissue distribution, bio-efficiency of a particular drug molecule and specifically combined with drugs having poor bioavailability. It also decreases the adverse effects drugs. Such bioenhancers are known as Yogvahi in ayurveda. Bioactive metabolites that are extracted from Piper species are used in discovery of novel drugs for therapeutic purposes. The review article aims to bring in to focus the antiviral and immunomodulatory properties of *Piper longum* and to encourage further evaluation of the plant based on these properties. The review article include information's collected from journals, internet databases, search engines and websites such as Science direct, Google Scholar, Scihub, Envis centre on medicinal plants.

2. Materials and methods

The information about traditional importance, pharmacological studies and isolation of phytochemicals of *Piper longum* were collected from Scopus indexed journal by using electronic search as Science Direct.

3. Result and discussion

3.1 Geographical and botanical distribution of *Piper longum*

Piper longum (Indian Long Pepper) (Figure 1) was found to grow in the tropical regions mostly the rain forests of India and other countries like Malaysia, Nepal, Sri Lanka, and Indonesia. In India, it originates from the evergreen forests of Central Himalayas, Assam, hilly regions of Mikir in West Bengal, Mount Kashi and found in the Western Ghats of Konkan Kerala, and islands of Car nicobar [1]. Soil that is sandy-loamy and well drained is best for *Piper longum*, also abundant in organic matter and strong in water retention.



Figure 1. *P. longum*

P. longum is a perennial shrub that has roots, usually woody and branches that creeps around as shown in Figure 1. The leaves are many and cordate and the blades are varying in size. On creeping and epiphytic branches the leaf blades are ovate or elliptic. Whereas on free branches the blades of leaves are ovate to ovate-oblong. Leaf blade is usually dark green in colour and measuring about 3-5 cm in width and 7-10.5 cm in length. Veination is opposite or alternate. While the flowers grow on solitary spike [2]. Flowers are monoecious and thus the spikes of male and female flowers are borne on separate plants. While the male spikes are thin, bract is orbicular and narrow stalked with 2 stamens, the female ones are circular and flat peltate bracts with 3 stigmas [3]. The fruit is very small about one inch in diameter, is sunk inside the spike. Fleshy fruits embedded in the spikes, attains red color when ripens and on drying becomes blackish green colored. The unripe spike is the Long pepper utilized for medicines. The portion of the root is usually thick and branched, is called Pippali-moolam. [4]

3.2 Traditional medicinal application

In Indian traditional medicine, *Piper longum* was used for treatment of respiratory disorders such as asthma, bronchitis, several stomach related problems such as dysentery, others including pyrexia and sleeplessness termed as 'insomnia' [5]. The fruit reported to be effective against parasites such as helminths, has heating effect, as an expectorant it clears mucus from lungs and other respiratory parts, act as carminative relieving flatulence, as well as stimulates the overall metabolism. *P. Longum* also improves stomach appetite and taste and much efficient in treating fever, inflammatory problems, infections of hemorrhoid, piles and discomfort or painful sensation in the abdomen. The stem was applied as decoctions to relieve the pain post delivery in mothers after child birth, and also useful in pains of rheumatoid arthritis and diarrhoea [6]. To treat toothache the fruit was externally applied. Moreover, the fruit was important remedy against distress of the intestines so tonic made out of the ripen fruits used as medicine. In India in cases of snake bites and scorpion stings the parts of the root and fruits of *P. longum* were used as nullifier or antitoxin against the venoms inserted into the body through stings [7]. Chinese system of medicines was depended on *Piper longum* fruits to treat chills in the stomach, nausea, acid reflux, headache and allergic rhinitis [8]. The leaves were grounded with little amount of water and this preparation was applied on to the chest of a person suspected with symptoms of breast cancer. The mature and unripe fruits of *Piper longum* were dried and had importance in traditional medicine of Thailand in relieving flatulence, have antidiarrheal activity, mucus clearing properties and relieving postlabor pain due to oxytocic properties [9]. The *Piper longum* was thus a reputed plant in the traditional system of medicine.

3.3 Antiviral potential of *Piper longum*

Viruses depend on the cellular processes of their host as they have limited proteins and enzymes of their own. Therefore the antiviral drugs are accepted slowly as the drug may affect the host cellular processes. Bioactive compounds extracted from plant sources have long been known as viral inhibitors. *Piper longum* has Ribosomal Inactivating Proteins (RIP) which has the ability to insulate against viral infection [10]. The effectiveness of *Piper longum* against several viruses has been recorded. Piper longum was found to have remarkable anti-Hepatitis B virus activity. Hepatitis B virus is basically a virus with double-stranded DNA, circular in form and belongs to the Hepadna virus family. The virus causes acute and chronic infection of the liver [11]. Although an effective Hepatitis B vaccine can prevent the infection however there is no effective treatment for the chronic infection which becomes a cause of concern owing to its high mortality rate. Piper longum when studied for anti-hepatitis activity showed inhibitory properties against Hepatitis B virus surface antigen (HBsAg) and Hepatitis B virus E antigen (HBeAg), as well as inhibitory to their secretions. [12] Antiviral assay of methanolic and chloroform extract of Piper longum seeds when evaluated against Vesicular Stomatitis virus and Human parainfluenzae virus on HeLa cell line exhibited significant antiviral activity [13]. The current scenario of Coronavirus pandemic 2019 (COVID-19) caused by the virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) has infected people all over the globe taking the lives of many. Coronavirus (COVID-19) is an RNA virus, it spreads through airborne transmission from droplets or discharge when an infected individual coughs or sneezes. The symptoms commonly are influenza-like symptoms such as dry cough, cold, fever, sore throat, and tiredness, shortness of breath, aches and pain. The infection can be mild to severe. Person with reduced immunity are at high risk of getting infected, if there is good immunity the infection may subside. There is an immediate need to find preventive and therapeutic agents that can reduce the symptoms as well as stimulate the immune system to combat these pandemics. Piper longum can be looked for such therapeutic properties as it has potential immunostimulating activity discussed further in this review, a much-needed attribute in these pandemics. Piper longum known as a Rasayana can control many infectious viruses or bacteria; it can also rejuvenate the cells and tissues in infected people and rapidly enhance their immunity [14]. Rasayana therapy is helpful in preventing the symptoms of COVID-19.

3.4 Immunomodulatory properties of *Piper longum*

Immunomodulators are substances which play a role in regulating the functioning of the immune system. Immunomodulators stimulate immune functioning and can modulate the various events of the immune system including the phenomenon of programmed cell death called 'apoptosis', synthesis of protein molecules that are important to immune functioning, and presentation, processing of antigens and target the regulation of various transcription factors and mediators of the immune system. Many plant extracts and their phytochemicals were known to boost the host's immune responses. Plants having a good proportion of phytoconstituents such as glycosides, alkaloids, oils, saponins etc. function as immunomodulators (Doshi et al. 2013). Immunomodulatory plants influence specific as well as non-specific branches of the immune system including both the innate and acquired systems. Such plants exert actions on the components of the immune system e.g. cytokines, interleukins, lymphocytes, natural killer cells, neutrophils etc. Piper longum containing most of the important phytoconstituents increases macrophage migration index and phagocytosis thus enhancing the resistance power of the host, can serve as an immunomodulator [15].

To validate the immunostimulatory activity of *Piper longum* fruits several tests were carried out by researchers such as the Haemagglutination titre (HA) test, Macrophage migration index (MMI), Phagocytic index (PI) in mice. *P. longum* was found to be effective for both specific and non-specific immunity subsequently at lower doses as reported [16]. To demonstrate the immunomodulatory ability, Balb/c mice were injected with alcoholic extract of *P. longum* fruit and piperine. The after-effects of injecting *P. longum* and its constituent piperine were studied and the overall impact on the

haematological parameter, bone marrow cellularity and α - esterase positive cells, circulating Ab titer, plaque forming cells were noted. The result of the studies were analysed and showed that injection of the extract of *Piper longum* and piperine increases the overall WBC (white blood cells) count in Balb/c mice which means they can stimulate the hematopoietic system and affected bone marrow cellularity and α - esterase positive cell showing an increase in such activities and thus indicating stem cell proliferation. The extract was found to increase plaque forming cells and cells contributing in producing antibodies and also antibody titer in circulation. This indicated that *P.longum* has stimulating affect on the humoral branch of the immune system [17].

3.5 Application of *piper longum* in Ayurveda treatment

Piper longum or Pippali known as Rasayana and is used in numerous Ayurvedic preparations (Kamboj, 2000) some of these formulations are reported below -

- **‘Trikatu’** is an ayurvedic formulation containing ingredients like Long Pepper, Black Pepper, and Ginger is used to treat various type of fever , abdominal distress, gastrointestinal tract problems ,bronchial discomfort, asthma and also effective as bioenhancer.
- **Vardhamanas Pippali rasayana** - is a preparation containing *Piper longum*, honey and ghee used to treats bronchitis, asthma, piles, splenic disorders, rheumatoid arthritis, and abdominal disease.
- **Talisapatradi Churna** – is a formulation of Black Pepper, Pepper longum, shunti, ginger important in treating respiratory distress, common cold symptoms such as cough, sensation of burns in palms, feet, constipation, abdominal pain and to stop bleeding from nose.
- **Pippalyedyesava** – is a formulation of Black Pepper, Long Pepper used for treating malabsorption, abdominal lump, piles, and anaemia.
- **Kanakasava** – is a preparation containing Piper Longum, Mulethi – Glycyrrhiza Glabra, Sonth - Zingiber Officinale, Shuddha Datura Panchang – Purified Datura Metal, Vasaka – Adhatoda Vasicas. It has ability to open airways of the lungs, relieves pain, antispasmodic, stimulates cardiac functioning, sleeps inducing and stimulates digestion.
- **Balacaturbhadrika** –contain ingredients such as Ghana (musta) -Cyperus rotundus, Krsna (pippali) – Piper longum, Aruna (ativisa) - Aconitum heterophy and Sringi (karkatasringi) - Pistacia integerrima . This formulation is efficient in the treatment of Diarrhoeal distress, Fever, Cough, cold and asthma like respiratory disorder.
- **Shringyadi churna** – contains Krsna (pippali)- *Piper longum*, Prativisa - Aconitum palmatu ,Sringi (karkatasringi) - Pistacia integerrim and is used for the treatment of asthma, diarrhoea, fever, cough, cold etc.
- **Amritarishta (also called Amrutharishtam)**- The medicinal extract prepared using *Tinospora Cordifolia* commonly known as Giloy , Kwath (Dashmool) and water then ingredients including Jaggery , cumin seeds , Long Pepper (Piper Longum) , Shahtra (Fumaria indica) , Nagkesar(*Mesua ferrea*) ,Sadona (*Astonia scholaris*) , Sonth (Zingiber officinale) , Black Pepper (*Piper nigrum*), Ativisha (*Aconitum heterophyllum*) , Mustak (*Cyprus rotundus*), Kutki (*Picrorhiza kurroa*), Indrayava (*Holarrhena antidysenterica*) seeds are mixed and kept aside for about a month for the process of natural fermentation to occur. This liquid is filtered and stored after a month. It is effective against typhoid fever, chronic fever, spleen enlargement termed as splenomegaly,

liver Enlargement termed hepatomegaly , gout , anemia, poor appetite , malaria, jaundice ,hepatitis infections , post delivery fever, ,rheumatic pains etc. The mixture boosts natural immunity as well as stimulates non-specific immunity and aids in fighting off bacterial, viral infections.

- **Guda-Pippalyadi Choorna** - contain ingredients such as Shunthi (*Zingiber officinale*) , Pippali (*Piper longum*) , Guda (Jaggery. Pippalyadi Choorna is effective in the treatment of insomnia (Verma et al., 2019).
- **Shiva gutika** – ingredients for the formulation include Shilajithu (Bitumen) , Shunti (*Zingiber officinale*), Pippali (*Piper longum*), Katuka (*Picrorhiza kurroa*), Karkatashringi (*Pistacia integerrima*), Maricha (*Piper nigrum*), Vidarikanda (*Pueraria tuberosa*), Talisapatra (*Abies webbiana*), Vamshalochana (*Bambusa arundinacea*), Patra (*Cinnamomum zeylanicum* leaves), Twak (*Cinnamomum zeylanicum* bark), Nagakesara (*Mesua ferrea*) , Ela (*Elettaria cardamomum*), Sesamum oil, Sugar, Ghee, Honey. Shiva gutika efficiently decreases the symptoms of cystic ovaries also improves the patient's condition. Thus can be effective in the treatment of Cystic ovarian diseases (Vishwesh and Dwivedi, 2014).
- **Kaishore Guggulu** – The formulation contain mixture of ingredients such as Guggul, Bibhitaki (*Terminalia bellerica*), Haritaki (*Terminalia chebula*), Amalaki (*Emblica officinalis*), Sunthi (*Zingiber officinale*, Amarta (*Tinospora cordifolia*), Marica (*Piper nigrum*), Pippali (*Piper longum*), Krmiripu (*Embelia ribes*), Danti (*Baliospermum montanum*, Tirivrt (*Operculina turpethum*). Kaishore guggulu has several properties such as antiallergic, antibacterial and blood purifying among the many attributes. It is considered to achieve healthy joints and muscles reduces fibromylegia, relieves back pain and. It acts as promoter of healthy and glowing skin, naturally cleanses blood, useful as herbal supplement in diet effectively treating conditions like diabetes, skin diseases etc. (Lather et al.,2011).
- Kumarysava – is an ayurvedic formulation contains Aloe vera as the major components and other minor components including Piper longum Ginger, Turmeric, clove, cardamom etc. Kumaryasava is recommended for curing lump formed in the abdomen, epileptic disorders, indigestion and menopausal problems (Manmode et al., 2012), (Johri RK et al., 1992, Singh R K et al 2012)

However, in Charaka Samhita Vimanasthana it is mentioned that Pippali should not be consumed in certain conditions and for long durations as it is a drug utilized in handling emergencies. Based on the frequency of usage it is both useful and harmful. When carefully used, promotes health beneficial characteristics otherwise it may be responsible for the aggregation of [18].

3.6 Phytoconstituents

Phytochemical studies conducted on the plant confirmed that the *P. longum* plant is a great source of major secondary metabolites such as alkaloids, flavonoids, steroids, essential oils, anthraglycosides, cardiac-glycosides, sterols, coumarins, anthraquinones ,arbutin, etc [19]. Pippali have a distinctive pungent flavour which is attributed to a major alkaloid present i.e piperine. It was estimated that about 4-5% of piperine is present in *Piper longum* [20]. Piperine contributes to most of the health promoting activities of the plant. Other important alkaloids are piperlongumine, pipernonaline, longamide, methyl piperine, piperettine, piperderidine, pipericide, asarinine, pellitorine, piperlonguminine, retrofractamide , N-isobutyl decadienamamide, brachyamide-A, dehydropipernonaline piperidine, and tetrahydro piperine, trimethoxy cinnamoyl-piperidine isolated from fruits and roots. Flavonoids present in the plant are epicatechin, catechin, quercetin, naringenin, kaempferol, myricetin, apigenin, and luteolin (Mustafa et al., 2010). The most prominent essential oil isolated from *Piper longum* are p- Caryophyllene, pentadecane, bisabolol , thujone, , a-Selinene p Selinene, p-cymene , Caryophyllene ,6-Cadinene oxide ,zingiberene, ,

methoxyacetophenone, α -Pinene, Sabinene, Myrcene, δ -3-Carene, dihydrocarveol, Limonene, β -Elemene, 6-Elemene, 9-Octadecene *oil*, α -Copaene etc. Lignans present are sesamin, pulvialitol, and fargesin. Organic acids such as palmitic acid and tetrahydropiperic acid, Esters commonly include eicosanyl-(E)-p-coumarate, Z-12-octadecenoic- glycerol-monoester and tridecyl-dihydro-p-coumarate, are present in *Piper longum*. With a large amount of these bioactive constituents present in it, *Piper longum* may serve for the development of the new pharmaceutical and therapeutic products.

4. Conclusion and future aspects

Our review presents information that may be valuable in screening of antiviral potential and immunomodulatory activity of *Piper longum*. Natural products with their bioactive compounds have always contributed to the development of drug molecules to cure various diseases. *Piper longum* is well established as medicinal ingredient with valuable pharmacological properties. There is strong ayurvedic and experimental evidences that validates its use to treat flu like symptoms such as cough, cold, fever etc. *Piper longum* serve as an immunomodulator. Immunomodulators can reduce the side effects such as immune suppression which presents the leading problems in other accustomed chemotherapy and radiation therapy. Use of target specific immunomodulator alongside chemotherapy holds potential clinical significance. *Piper longum* is easily available in Indian households and proper knowledge among people related to its usage can contribute to promoting health amidst the pandemic. *P. longum* used in traditional medicine is mixed with several alternative plants having medicinal attributes. Therefore, the reciprocal action of all the additives in the mixture of medicine as well as their combined effect should be evaluated. Moreover *Piper longum* has also been reported to improve the efficacy as well as reduce adverse effects of drugs and thus has the potential to be combined with synthetic agents used in modern medicine. However, it is also mentioned in the review that Pippali should not be consumed in certain conditions, so the safety profile evaluated rigorously. The gap between ayurvedic evidences and scientific experimentation that validates the immunomodulatory and antiviral potentials needs to be bridged by extensive screening of *Piper longum*.

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