REVIEW ON ANTITUSSIVE PROPERTIES OF TERMINALIA CHEBULA (HARAH) HERBAL DRUG

Ankit Kumar*, Vandana Sahani and Shivanand Patil

Department of pharmacy, Shree dev Bhoomi institute of Education Science and technology, Poundha, Dehradun, Uttarakhand -248007
Email id: ak4925173@gmail.com

ABSTRACT

The two forms of cough are defensive reflexes, one of which is more responsive to mechanical stimulation and the other to chemical stimulation from substances including sulfur dioxide, ammonia, citric acid, and capsaicin. There is some proof that suppressor therapy works best when used to reduce coughing in the short term. The use of herbal medications for a variety of illnesses, including those requiring antitussive activity, is expanding globally today. The study's objective was to examine the antitussive properties of various extracts, fractions, and constituents of the medicinal plants under investigation. Massive global problems are posed by the emergence and spread of novel infectious diseases that are both bacterial and viral in origin. In both the present and the past, respiratory illness has been one of the main worries. There is a need for effective herbal medicine to treat infectious diseases because there is a lack of a safe and effective vaccination and small molecule pharmaceuticals for effective therapies. The herbal remedies indicated in Ayurveda are a great place to start when looking for a cure. Ayurveda's promising herbs for immunmodulatory and respiratory health were used in the current investigation to make a hard-boiled candy formulation. antitussive activity depending on the dose. This activity was comparable to the prototype antitussive agent diphenhydramine HCl. The data clearly shows that a higher dose of 3 ml is more effective. It was found that the antitussive activity produced by the herbal formulation at minimal doses was much better than that of standard drugs. Herbal medicines mentioned in the scriptures for treating respiratory infections are better than modern medicines such as cough suppressants, expectorants, mucolytics, etc. because they have no side effects.

The herbs chosen were Piper longum (fruits), Glycyrrhiza glabra (roots), Curcuma longa (rhizomes), Zingiber officinale (rhizomes), and Ocimum sanctum (leaves).

INTRODUCTION

The cough reflex represents the most important defense mechanism Airway reflexes, together with the mucus transport system, constitute the main mechanism for clearance respiratory tract. [1] Coughing protects the respiratory tract from congestion, preventing mucus from becoming infected falling into the lungs and bronchi, is possible very dangerous. The cough reflex is one of the most common symptoms of diseases of the respiratory system and is the most common reason sick patients seek medical care [2, 3] Pathological cough has a significant impact on the patient's quality of life, observed in the field of physical functioning or the psychosocial field. Current treatments are often limited by a lack of effective drugs. In addition, most of the drugs available can cause unavoidable side effects clinical features Natural products are invaluable as biologically validated platforms for drug development [4–6]. Indeed, a series of review articles have demonstrated the continuing and valuable contribution of nature as a source of lead compounds as a basis and inspiration in the synthesis of new drugs [7, 8]. Terminalia chebula, a medicinal plant belonging to the genus Terminalia (family: Combretaceae), is grown in Tibet, Taiwan, China and India [9, 10]. The ripe and dried fruit of T. chebula, known locally as haritaki, has been widely used to treat fever, sore throat, cough, vomiting, hiccups, bleeding, hemorrhoids, diarrhea, gout and heart and bladder diseases. [11]. Therefore, the aim of this study is first of allcharacterize the polysaccharide of T.chebulafruit. Furthermore,theantitussiveactivityoftheisolated polysaccharide in terms of cough frequency and specific airway resistance under in vivo conditionsin the awake male TRIK strainguinea pigs were evaluated.

For thousands of years, sophisticated traditional medical systems have been built on the foundation of plants [12]. Systems based on Ayurvedic, Unani, Kampo, and traditional Chinese medicine continue to be crucial in primary healthcare [13]. The World Health Organization (WHO) estimates that 80% of the world's population, who are primarily residents of developing countries, rely on traditional medicine, and that 85% of traditional medicine uses plant extracts or their active ingredients.

The health care systems of the remaining 20% of the population, who mostly live in wealthy nations, also heavily rely on plant-derived goods. For instance, from 1959 to 1980, 25% of all prescriptions filled at neighborhood pharmacies in the USA contained plant extracts or active ingredients made from higher plants [14].

The majority of widely used cough medications are based on herbal extracts. There are countless plants that have been approved as antitussives by various bodies. For instance, more than 100 herbs are classified as antitussives in the USA Physician Desk Reference (PDR) for Herbal Medicine [15]. Folk medicine has long employed opium, ammi, coltsfoot, plantain ma huang, thyme, and other substances to treat coughs and other respiratory conditions.
In the botanical and ethnopharmacological literature, there have been several reports that traditional antitussive plants from Europe, Asia, Africa, and other places may have strong cough-suppressing effects (for example, see [16-18]).

The Terminalia chebula Retz. (family Combretaceae) tree is indigenous to the subcontinent and is locally referred to as "Harh" or "Harir" in Urdu and Punjabi [19]. The fruits of Terminalia chebula are used as stomachic, tonic, carminative, expectorant, anthelmintics, antidysenteric, alternate, and antispasmodic remedies in ayurveda and unani medicine.[20] These are helpful for conditions such as diabetes, dysentery, anemia, bronchitis, chronic and recurrent fever, cough, sore throat, thirst, vomiting, inflammation, tumor, bleeding piles, and eye problems. In an asthma attack, fruits that have been roughly pulverized and smoked in a pipe can be helpful [21]. In compound formulations, Terminalia chebula provides a great remedy for the alleviation of phlegmatic disorders [22].

Experimental animals can be made to cough by either stimulating the central nervous system (CNS) or by pharmacological, mechanical, or electrically stimulating sensory nerve afferents in the larynx, trachea, or bronchial mucosa. The cough induced by chemical stimulation is thought to be closer to that of a person than that induced by other tussigenic stimuli. [23]

The History of Chebula

For internal use, chebula is best known as one of three fruits that comprise triphala, a go-to Ayurvedic herb combination that's used to treat everything from digestive issues to diseases and has been employed by practitioners for millenia. The combo is sold in pill, tincture, and powder formats, as well as whole dried berries. Gaia herbs notes that "Haritaki is used in Ayurvedic medicine to promote healthy vision, brain function, and even longevity," as well as "a bowel regulatory tonic and gentle laxative."

Terminalia chebula, commonly known as **black-** or **chebulic myrobalan** is a species of *Terminalia*, native to South Asia from Pakistan, India and Nepal east to southwest China (Yunnan), and south to Sri Lanka, Malaysia, and Vietnam.

Scientific classification

Kingdom: Plantae
Clade: Tracheophytes
Clade: Angiosperms
Clade: Eudicots
Clade: Rosids
Order: Myrtales
Family: Combretaceae
Genus: Terminalia
Species: T.chebula
Binomial name: Terminalia chebula

Extraction preparation

Each collected plant material (two kilograms) was dried in the shade, ground into a coarse powder, and then macerated separately in four liters of a water-ethanol mixture. Following a 7-day maceration period, the entire extract was removed and vacuum-concentrated using a rotating vacuum evaporator [24] The resulting residue was stored in a dessicator for future research.

manufactured cough medicine

Physical and chemical properties including density, pH, refractive index, alcohol content, and acid value were assessed in accordance with the Indian Pharmacopoeia's recommended methodology. In addition, the color, smell, and taste were noted [25] as shown in table -1.

Table 1: Physicochemical parameters of formulated polyherbal cough syrup

Colour	Reddish brown
Odour	Sweet Aromatic
Taste	Sweet
Specific Gravity	1.25
Density	1.37
Refractive index	1.54
Ph	4.8
Acid value	0.118

DETERMINATION OF PHARMACOLOGICALS

Animals

From the TPC (the pharmaceutical college), Barpali animal house, thirty healthy guinea pigs (300–400 g) of either sex were chosen. They were housed in the departmental animal house for a week before to and after the trials under the following lighting conditions: 14 hours of light and 10 hours of darkness, 27 2°C, and relative humidity of 44–56%. They were given a conventional food to eat, and they had unlimited access to water. All animals were handled in accordance with Institutional Animal Ethical Committee approval and the most recent regulations1.

Antitussive activity

The method described by [26] was adopted to evaluate antitussive activity.
The animal were divided into five groups of six each
Group- **I** control group
Group -**II** received diphenhydramine hydrochloride (2.8mg/kg)
Group -**III** received 1ml formulated cough syrup
Group -**IV** received 2 ml formulated cough syrup
Group **-V** received 3 ml formulated cough syrup
Two tubes were attached to the ends of a cylindrical glass jar that contained the animals. The aerosol enters through one and exits through the other. The latter tube has a side arm that connects to a tambour, which allows for the measurement of pressure changes. On the efflux tube beyond the side arm, a pinch clamp with a variable screw was installed, allowing the system's sensitivity to be adjusted so that the displacement of air in the cage brought on by the animal's coughing could be detected. For ten minutes, the guinea pig was exposed to an aerosol of 7.5% citric acid in water. The control reaction was initially evaluated on each animal.

Statistical analysis

All the data are expressed as mean ± SEM. The values obtained for the above parameters were compared with standard and control group using one way ANOVA followed by Student’s testThe values of $p < 0.05$ and $p < 0.001$ were considered to indicate a significant difference between the groups.

PHARMACOLOGICAL ACTIONS

Anti-bacterial activity

Terminalia chebula is proven to be an effective anti-bacterial agent. Amongthe ether, alcohol and water extracts of T.chebula , ether extract was found to be very effective with Minimum Inhibitory Concentration and Minimum Bacteriocidal Concentration[30].Terminalia proves to be an effective anti-bacterial agent by forming the inhibitory zone against Pseudomonas aeruginosa,P. fluorescens, B. bronchiseptica, S. aureus, S. epidermidis, B. cereus and B.pumilis[31].Terminalia was found to be effective against both gram- positive and gram-negative bacteria and was confirmed to act as an excellent antimicrobial agent against the tested organisms such as Bacillus subtilis, Proteus vulgaris, Salmonella typhimurium , Pseudomonas aeruginosa, Escherichia coli K-12 and Staphylococcus aureus [32].

Anti-cancerous activity

Terminalia is proved to an possess anti-cancerous activity. The 70% methanolic extracts of the plant against five different cell- lines such as human prostate cancer cell line (PC-3), human (MCF-7) and mouse (S115) breast cancer cell lines human osteosarcoma (HOS-1) and a non-tumorigenic, an immortalized human prostate cell line (PNT1 A) was tested. The compounds responsible for cytotoxic activity such as chebulinic acid, ellagic acid and 2,4- chebulyl-b-Dglucopyranose was also isolated. The highest activity was shown on PNT1A cell lines and PC3 cell lines.[33] The compound chebulagic acid was evaluated for its capacity to inhibit the growth of the five cell lines such as MDA-MB-231 (breast carcinoma), HCT-15, COLO-205 (colon cancer), DU-145 (prostate cancer) and K-562 (chronicmyeloid leukemia) and was found to be positive [34]. Chemomodulatory effect of Terminalia chebula against the nickel chloride was tested with the methanolic extract on Wistar rats and was found out that the given extract downregulates the GSH, and GR activities [35] Another study was made on the ability of Triphala to inhibit Cytochrome P450. They found that the inhibitory activity against CYP3A4 had IC50 values of <0.1 mg/ml for ethanol [36]. Mice grafted with human pancreatic tumours fed the Triphala formulation showed the reduction in the size of the tumours to half the size of those in a control group of mice that were fed with saline [37].

Anti-fungal activity

Terminalia chebula is expected to act against the fungal infection. A study was conducted on the anti-fungal activity of Terminalia sp. In that study aqeous, ethanolic and alcoholic twig extracts were tested against the fungal strains Alternaria brassicicola. A. alternata ,Helminthosporium tetramera , Aspergillus flavus and A. niger. Results showed that aqeous extracts were not much effective. Alcoholic extracts showed better inhibition than aqeous and ethanol extracts. It is also found that A.niger was better inhibited by T.chebula.[38] Another study was made on the inhibitory action of 42 methanolic plant extracts including the above plant over the Clotrimazole-resistant Candida albicans and Aspergillus flavus and was found that the methanolic extract of Terminalia chebula unripe seed inhibited the fungal infection [39].

Anti-diabetic activity

Terminalia was found to have anti-diabetic activity. The extracts of Terminlia for its anti-hypoglycemic and anti-diabetic activity was conducted against the advanced glycation endproducts (AGEs)-induced endothelial cell dysfunction and was found out that the treatment of chebulic acid reduced glycer-AGE induced formation.[40] The methanolic and ethanolic extracts of the plant was found to reduce the glucose levels. [41]

Anti-inflammatory activity

Anti-inflammatory activity was expected to be present in T.chebula and was tested in the Swiss albino mice . Triphala treatment was found to significantly inhibit the paw volume and also the levels of lysosomal enzymes, lipid peroxidation and inflammatory mediator tumour necrosis factor-α. However the anti-oxidant status was found to show a increase in the plasma, liver and spleen of monosodium urate crystal-induced mice on comparision with the control mice.

ß-glucuronidase and lactate dehydrogenase level were also found to be reduced in Triphala treated monosodium urate crystal-incubated polymorphonuclear leucocytes. Results obtained from the above studies clearly indicated that Triphala possess a strong anti-inflammatory effect against gouty arthritis.[42]

Anti-typhoidal activity

The Aqueous extract was evaluated for its ability to reduce the risk of typhoid fever in Swiss albino mice. The extract was found to exhibit anti -salmonellae activities against S.typhi and S. typhimurium by means of the clear zone of inhibition. Terminalia acts both as the bacteriostatic and as the bactericidal agent.[43]

Anti-oxidant activity

T.chebula is found to be an excellent anti-oxidant. The aqueous extract of Terminalia chebula was tested for its potential antioxidant activity by means of its ability to inhibit gamma-radiation-induced lipid peroxidation in the tested rat liver microsomes and the damage to superoxide dismutase enzyme in rat liver mitochondria. On irradiation, the activity of the enzyme was found to be decreased which proves the restoring activity of the enzyme to a great extent. These studies confirms that the extract of T. chebula was able to protect the antioxidant enzyme from the effect of the reactive oxygen species that is produced by gamma radiation.[44] The methanol, water and 95 % ethanol extracts from Terminalia chebula were found to have the greater antioxidant activities. The higher antioxidant activities were observed in the methanol and 95 % ethanol extracts of Terminalia chebula.[45] The ethanolic extracts of the frtuits of Terminalia was also tested to know its anti-oxidant activity in albino rats and was found to decrease the levels of lipid peroxidase.[46] T. chebula have the capacity to show the protection against the photosensitization-induced oxidative damage as they show their ability to prevent the process of Fe(II)-induced lipid peroxidation that might be inturn useful in reducing the photo-induced iron toxicity.[47]

Anti-viral activity

Terminalia was found to possess an excellent anti-viral activity against the cytomegalo virus. The hot water extract of the plant inhibited the Plaque formation of HCMV without depending on the dosage. Anti-HCMV or antiMCMV activity was found out at the much lower concentration and was determined that Terminalia chebula significantly suppressed the CMV yields in the lungs of cyclosporine-treated mice on comparision with the water treatment.[48] The study performed with T. chebula extracts on combination with the acyclovir against herpes simplex virus 1 showed their anti-HSV-1 activities very strongly.[49] Terminalia was found to be the potentially inhibitor of swine influenza virus. The acetone extract of Terminalia chebula Retz could be considered as the effective method for human being who are fighting against pandemic swine influenza A virus due to its low cost, easy preparation and significant therapeutic potential. [50]

Cardioprotective activity

Terminalia has been proved to be a efficient cardioprotective agent. The alcoholic extract of T. chebula (TCE) pretreatment in order to attenuate the isoproterenol induced alterations on the heart mitochondrial ultra stucture and function in the experimental rats was investigated. TCE pretreatment provided significant protection against the metabolic alterations induced by the ISO (isoproterenol). [49] Another study was conducted to evaluate the therapeutic efficacy of T.chebula in the protection against the isoproterenol induced lysosomal membrane damage which was found to be positive. The study confirmed that the pretreatment with T chebula extract has partly impart its cardioprotective effect by means of the lysosomal membrane stabilization and thus prevents the myocardial necrosis.[51]

Anti-caries activity

The aqueous extract of Terminalia chebula was investigated for its ability to inhibit the growth and physiological functions of Streptococcus mutans. The aqueous extract of T. chebula was found to possess the antibacterial activity against S. mutans with the Minimum Inhibitory Concentration. Mouth rinsing with the solution of the extract of T. chebula brought resulted in a significant reduction in the total salivary bacterial count as well as the total streptococcal count. This proves that the extract of T. chebula can be used as an effective agent for the treatment of carious teeth because of its ability to inhibit the growth and accumulation of S. mutans on the tooth surface which would prevent the accumulation of acids demineralization and the breakdown of the tooth enamel.[52]

Radioprotective activity

The aqueous extract of triphala was administrered intraperitoneally to study the radiation-induced mortality in the mice that were exposed to γ-radiation. The study found out the fact that the optimum radioprotective dose of 10 mg/ kg the T. chebula was found to be 1/28 of the LD50 dose (280 mg/kg b.wt.), which was found to be far below the LD50 dose.[53]

Wound healing

: The hydroalcoholic extract of T.chebula fruit was tested for its wound healing activity in the alloxan induced diabetic rats by using the excision and dead space wound models which showed a significant increase in the wound healing activity in the fruit extract treated rats. The T.chebula extract was found to promote the healing of wound contraction in alloxan induced diabetic rats when applied topically by means of increasing the rate and extent of wound closure[54]. The wound healing activity of the ethanolic extract of fruit of Terminalia chebula was also evaluated on excision and incision model in the albino rats in the form of an ointment.[55]

Anti-ulcer activity

The anti-ulcer activity of the methanolic extract of Terminalia chebula fruits was evaluated in the pylorus ligation and ethanol induced ulcer models of the wistar rats proved them to be a potent anti-ulcer agent. [54,56,57] Histopathological changes observed on the pylorus ligation model has showed the degeneration, hemorrhage, edematous appearance of the gastric tissue.[58]

Other uses

Terminalia was used for microbial transformation process which uses the tannase and gallic acid production by means of the the co-culture technique from the tannin-rich substrates [59] Terminalia was also found to possess anaphylactic activity. Passive cutaneous anaphylaxis was inhibited by Terminalia which was given by oral administration. Terminalia pretreated models showed the serum histamine levels getting reduced in a dose-dependent manner. Terminalia also inhibited the histamine release from rat peritoneal mast cells.

CHEMICAL COMPOSITION

T. chebula contains 32% tannin. T. chebula comes from pyrogallol (hydrolyzed) type, they contain 14Hydrolyzed tannins (gallic, chebulic acid acid, punicalagin, chebulanin, corilagin, neo-chebulinic ellagic acid, chebulegic acid, chebulinic acid, 1,2,3,4,6-penta-Ogalloyl-ß-D-glucose, 1,6-di-O-galloyl-D-glucose-casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin) Tannin content varies according to geological changes. Flavonol glycosides, triterpenoids conjugated coumarins with gallic acid called chebulin, as well as phenol compounds have also been isolated [60] In addition, ethyl gallate and Luteolin was isolated from the fruit of T. chebula [61]. It also contains many nutrients such as vitamin C-proteins, amino acids and minerals.[62] Exploit T. chebula

Alcohol extraction

The dried fruits of T. chebula are ground into separate powder and 100g powder taken twice in 500ml 75% methanol by stirring overnight and centrifuging at ambient temperature. Then, the supernatant was collected and Evaporated to dryness under reduced pressure in a rotary mill Evaporator. The extract is dissolved in water and used in in vivo and in vitro experiments [63]

Water extraction

Finely powdered dried fruit (20# mesh) of T. chebula is stirred with eight parts distilled water about 70 to 80°C for 2 hours. The liquid extract was then filtered through a sieve (200# mesh). After that, the filtrate is obtained gathered into two parts on a rotating vacuum Evaporator. Finally, the concentrated liquid is dried to obtain dry powder extract. Concentration is expressed as µg/ml. [64]

Terminalia chebula recently used in the following formulations

- Triphala churna
- Antussive polyherbal cough syrup
- Herbal mouth wash
- Herbal gel
- Abhayaristha syrup
- Cosmetic cutaneous wound healing
- Antacid anti-ulcer suspension
- Antidiabetic churna
- Eye drug (Kajal)
- Poly herbal film coated tablet
- Herbal hair dye
- Cracked feet pastes

PHARMACOLOGICAL AND BIOLOGICAL USES

T. chebula is called the “the king of medicines” in the J. Med. Plants Res. Tibet is known for its incredible therapeutic properties, which have a broad range of biological and pharmacological applications including antiviral, antibacterial, antifungal, and antimutagenic hypolipidemic, anti-anaphylactic, and adaptogenic reduced cholesterol, improved motility of the gastrointestinal tract and hepatoprotective, cardioprotective, anti-ulcerogenic, antidiabetic, retinoprotective, and radioprotective antispasmodic, purgative, immunomodulatory, and wound healing chemically preemptive.[65]

T. chebula's antioxidant activity

An examination using high performance liquid chromatography (HPLC) verified the presence of phenolic chemicals in the fruit of Terminalia extract. The ability of the extract to deactivate free radicals, such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals, has been investigated because these substances are effective free radical scavengers. A stable free radical, DPPH has a maximum absorption wavelength of 517 nm. When there are chemicals present There is a drop in absorption at 517 nm because the substance is no longer capable of scavenging hydrogen (H) atoms or electrons, hence losing its free radical status. The decline in DPPH absorption has been observed at different extract concentrations (3.5 to 23 μg/ml), and it is evident that the absorbance caused by DPPH constantly declines up to 23 μg/ml [65]

Acid gallic

Whether free or esterified, gallic acid (3, 4, 5-trihydroxybenzoic acid;) is one of the primary endogenous phenolic acids present in plants. It has been discovered that gallic acid is a pharmacologically active substance with hepatoprotective, antioxidative, antimutagenic, and anticarcinogenic properties. It has been observed that the primary metabolite of gallic acid is 4-Omethylgallic acid. There have also been reports of other minor metabolites, including 3-O-methylgallic acid, 3- 4-O-dimethylgallic acid, and pyrogallol (conjugated and unconjugated forms). The best medications for avoiding and suppressing inflammation brought on by chemical, mechanical, infectious, and immunological stressors are glucocorticoids. The binding of glucocorticoids to their receptors, which causes either activation or repression, is one of the main ways that they exert their action.

Usage in cosmetics

Decrease in melanin

Kojic acid, a depigmenting agent, has been shown to have carcinogenic properties. Therefore, safe agents such as T. chebula plant extract should be developed for use in cosmetics as a depigmenting ingredient. T. chebula extract has a lot of promise as a secure and reliable depigmenting agent. At 100 ppm, the T. chebula methanolic extract exhibited a melanin inhibiting activity of greater than 90% [66].

Inflammatory-reduction action

One of the primary endogenous phenolic acids present in the T. chebula plant, which has anti-inflammatory properties, is gallic acid (3, 4, 5-trihydroxybenzoic acid) [67].

Cell-based ageing

Cellular aging was significantly inhibited by the ethanol extract from T. chebula fruit [68]

Astringing

T. chebula extract is utilized as an astringent in allopathy [69]

Unspecified uses

It is employed as a blood purifier in the Unani system. The fruit pulp can cause piles, intestinal worms, ascites, chronic diarrhea, dysentery, costiveness, flatulence, asthma, urinary disorders, vomiting, hiccups, and enlarged liver and spleen.[70] The Latin word "modere," which means to nibble, is the source of the English word "mordant," as it nibbles a substrate's surface and aids in the fixing of a dye on the substrate. According to [71] T. chebula leaves and fruits are also utilized as a mordant.

Conclusion

The present study indicates that extract of Terminalia chebula possesses antitussive activity against sulphur dioxide gas evoked cough in mice. This activity of the plant was partly reversed by naloxone, but it was not affected with treatment by rimcazole, indicating a partial involvement of opioid receptors in inhibition of coughing. In addition, the antitussive potential of this plant correlates with various pharmacological properties, which may justify its widespread use in various respiratory conditions in traditional medicine. Further studies aimed at isolation of the active compounds responsible for antitussive activity are ongoing in our laboratory.

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