

Review Article

Comprehensive Review on Targeting Cough Reflex Pathways Using Plant-Based Therapeutics

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A B S T R A C T

Cough hypersensitivity is a complex neurophysiological condition involving both peripheral sensory pathways and central neural processing and is often exacerbated in respiratory diseases. Despite the availability of synthetic antitussive agents, their limitations, including adverse effects and variable efficacy, necessitate the development of alternative therapeutic strategies. Plant-based polyherbal formulations offer a promising multi-target approach due to their diverse phytochemical composition and synergistic pharmacological actions. This review explores the therapeutic potential of a formulation comprising Amla (*Phyllanthus emblica*), black pepper (*Piper nigrum*), ginger (*Zingiber officinale*), honey, Bharangi (*Clerodendrum serratum*), Pushkarmool (*Inula racemosa*), and Kantakari (*Solanum xanthocarpum*). These agents collectively modulate cough reflex pathways through anti-inflammatory, bronchodilatory, demulcent, antimicrobial, and bioavailability-enhancing mechanisms. The synergistic interplay of these constituents enables comprehensive management of cough by targeting airway inflammation, mucus hypersecretion, and neural hypersensitivity. This study underscores the potential of integrating traditional knowledge with modern pharmacology to develop safe and effective antitussive therapies.

Keywords: Polyherbal Formulation, Antitussive, Traditional Medicine, Ethnopharmacology, Cough Reflex

Introduction

Coughing is a protective reflex of the respiratory system that reduces the infection through the respiratory tracts and also helps to keep the airways clear. The sensory receptors present in the respiratory tract stimulate the cough reflex by passing the signals through neural pathways that connect to the brainstem. However, coughing is a sensory reflex

that protects the lungs and airways, the excessive and chronic reflex is a sign of a bigger problem and can cause discomfort and other respiratory issues.¹

Respiratory disorders are pandemic and communicable diseases in all over the world, especially in developing countries due to a lack of medical care. Coughing is a stage one symptom of all respiratory diseases, such as

tuberculosis, influenza, pneumonia, and recent viral infections. In these medical conditions, the protective reflex due to the lining of the airways is inflamed and irritated. At the same time, coughing is a major factor in the spread of disease through infectious droplets into the air, which may raise the risk of spreading diseases within communities.^{2,3}

Coughing can affect the body in many ways. Repeated coughing can irritate the lining of the lungs, throat irritation, pain on chest, wear out the muscles and cause mucosal bleeding. Sleep disturbances and breathing discomfort are common disadvantages, especially in children with chronic cough. Some of the severe complications, like syncope, haemoptysis, or elevated intrathoracic pressure, may rise due to coughing. Chronic cough slightly effects the mental health as well as the physical health of the patients. It makes people to get anxious, embarrassed in social situations, and lower their quality of life.⁴ These effects explain to us the importance of cough management in a safe and effective manner, especially in contagious diseases, while controlling symptoms help to decreases or prevent the spread of the disease.

Antitussive agents are common medicines used to treat coughs. They may act on both the central and peripheral system. These medications can help to treat the symptoms, but they may cause some of the side effects like sedation, tolerance, and the risk of addiction. Additionally, recent studies and research uncover that the effectiveness of drugs may differ based on the underlying aetiology of cough, especially in chronic or infection-related scenarios.⁵ These demerits lead to a change in the researchers focus to alternative medicines and therapeutic methodologies. Mainly, the multi-target action, plant-based therapies may provide broader activity compared to conventional dose and single-target drug delivery.^{6,7} In addition, herbal remedies are generally considered for their low toxicity and side effect also have more accessible and better tolerated, particularly in resource-limited settings. The history of traditional plant use, combined with scientific development and the highlights their potential role in modern healthcare developments. Therefore, conducting studies for the need of systematic evaluation of medicinal plants with antitussive properties, particularly in the context of respiratory and communicable diseases.^{8,9} The plant-based therapies are safer and effective alternatives for cough management.¹⁰

Pathophysiology of Cough

The cough reflex starts with mechanical or chemical stimuli of sensory receptors present in the airways of the respiratory tracts. C-Fiber receptors are activated by chemical stimuli like prostaglandins, histamine, and

bradykinin, which are responsible for cough, and adapting receptors rapidly activated by mechanical irritation like dust or allergens. The afferent signals are carried by the vagus nerve nerve to medulla oblongata where the cough centre is aligned. Efferent signals are sent to the diaphragm, intercostal muscles, laryngeal muscles, and respiratory muscles after signals are centrally processed then produce cough. Coughing reflex starts by deep breathing, then closing glottis will increase the pressure inside the chest which may result in strong exhalation that quickly expel the irritants by forceful expiration. In pathological states, inflammation or infection may induce continuous activation of cough receptors causes hyper-sensitive, chronic cough and condition-like tissue or mucosal irritation. The interaction between peripheral sensory receptors, central neural circuits, and coordinated muscle activity result in complicated cough reflex.^{11–14} The Cough Reflex Mechanism pathway is given in Figure 1.

Mechanism of Antitussive Activity

The mechanism of action of antitussive agents are mainly to reduce or control the cough reflex by acting on both the central and peripheral nervous systems. Centrally acting drugs act on medulla oblongata to control hyperresponsiveness, such as the cough reflex. Peripherally acting agents decrease the response of cough receptors in the respiratory tract and prevent the transmission of afferent nerve impulses. Demulcent agents protect the mucosal lining of the throat and reduce receptor stimulation and irritation. antitussives reduce inflammation in the airway by relaxing the smooth muscles in the bronchial tube. The combination of both actions together will suppress the cough reflex pathway and prevent coughing.^{16–18}

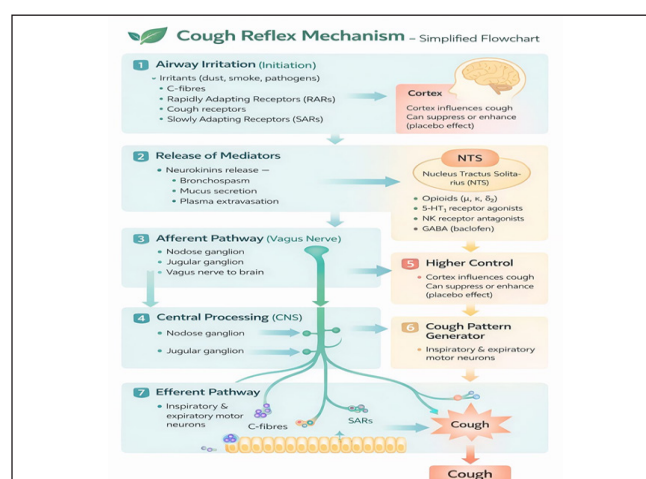


Figure 1. Airway Irritation and Neurophysiology of cough reflex pathway

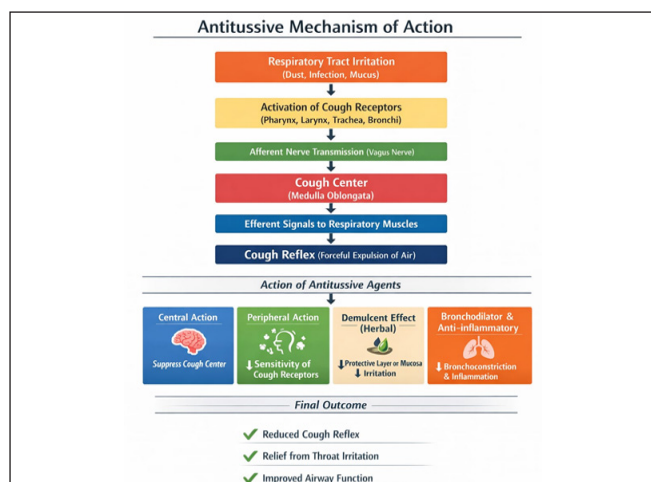


Figure 2. Mechanism of Action of Antitussive Agents in Cough Reflex Suppression

Traditional Medicine

Traditional medicine is an ancient method that consists of a wide range of medical knowledge and practices that have changed over time with different cultures. This methodology based on real-life practical observations, traditional beliefs, and hands-on experience. Traditional medicine is used the prevention, diagnosis and treatment of diseases as well as promoting health and health care system. This system of medicine contains Ayurveda, Siddha, and Traditional Chinese Medicine, as well as many indigenous healing traditions followed in different parts of the world, which still being practiced and kept alive.

Traditional medicine improves health by balancing the body, mind, and environment. This is the most important strategy used in traditional medicine to treat disease. Traditional systems which is different from conventional methods that often focus on restoring overall balance and improving the body's natural ability to heal the condition. The natural materials, such as plants that are good for you, minerals, and substances that come from animals are used as therapeutic interventions. Among these, plant-based preparations and medicine are the most important part in many of the basis traditional recipes.

Depending on their uses and need, traditional medicines are made in different procedures and methods. Some of the common forms of medicine are decoctions (kashayam), powders (churna), tablets (vati), syrups (asava/arishta), medicated oils (taila), and semi-solid preparations like avaleha, which are used to treat coughs and other respiratory issues. Traditional medicine is still playing important role in the healthcare system around the world, especially in developing countries because of lack of facilities in modern medical. People still use traditional medicine because of their availability, cheap, less side effects and culturally accepted.

In many primary healthcare system traditional medicine used as first line of treatment.^{18,20} Researchers have found newer active compounds that have many possible medicinal values and also responsible for therapeutic effects, especially in areas like respiratory problems, inflammation, irritation and immunity. This encourages to search for new drugs used as traditional medicine.

There has been a renewed scientific interest in traditional medicine in recent years, particularly regarding drug discovery and development. Numerous bioactive compounds and phytoconstituents derived from traditional plants have contributed to the development of modern pharmaceuticals, underscoring their therapeutic potential^{21,22}.

Plant Description

Amla

The Amla (*Phyllanthus emblica*) belongs to the family Phyllanthaceae, genus Phyllanthus, and species emblica, and is a medicinal fruit. The fruit is almost globular in shape, bearing a sleek surface of pale greenish-yellow, marked by distinctive longitudinal furrows and delivering a sharp, astringent flavour with a sour undertone. Microscopic investigation shows an outer epidermal layer coated with a cuticle. mesocarp is densely packed with parenchymatous cells. These cells are abundantly loaded with tannins, and sclereids interspersed throughout the tissue. Vascular bundles are irregularly dispersed within tissue. Flourishing across the tropical and subtropical regions of India is filled with this fruit, possessing antitussive doses ranging from 3–6 g as powdered preparations.²³

Black Pepper

Black pepper (*Piper nigrum*) belongs to the Piperaceae family. The pepper comprises sun dried, immature tiny berries with black color and distinct spicy flavour. Microscopic examination of the fruit reveals a clearly defined pericarp. It also contains an epicarp, a mesocarp enriched with oil cells and stone cells, and an endocarp. The seed contains dense starch granules and protein bodies. Black pepper is predominantly found in the damp regions of Southern India with a dose of 1–3 g.²⁴

Ginger

The rhizome of ginger (*Zingiber officinale*) belongs to the Zingiberaceae family. The root of the Ginger plant is buff-coloured, aromatic, and taste very pungent. Microscopically, the layer of cork with abundant starch grains, scattered vascular bundles, and oleoresin cells are filled by parenchymatous tissue are bundles and special cells that contain oil. It is widely cultivated in warm regions of India, such as Kerala and Assam. The usual dose for antitussive activity ranges between 1 and 2 g.²⁵

Honey

Honey is a natural product produced by *Apis mellifera*. This belongs to the family Apidae. This is a yellow, viscous liquid with a sweet taste and pleasant odour. The Microscopy section reveals pollen grains and wax. Sugar crystals are also visible at times. Honey is widely used across India with good production. It is commonly used in doses of honey for antitussive activity ranges between 5 and 10 ml.²⁶

Bharangi

The root of Bharangi (*Clerodendrum serratum*) is generally brown and cylindrical with a rough surface. It belongs to the family Lamiaceae. Microscopically, it shows cortical cells and a cork layer. Medullary rays are distinct with well-developed secondary xylem. It is widely distributed in the foothills of tropical and subtropical regions in India. The root is used for antitussive activity as traditional formulations with a dose range of 3-6 g.²⁷

Root of Pushkar

Pushkar is a root that comes from a plant called *Inula racemosa* which belongs to Asteraceae family. The key characteristic of the root is thick, cylindrical shape with a characteristic odour. The transverse section of this root exhibits cork cells, cortex with secretory ducts, and well-developed vascular tissue with xylem. It is predominantly found in Himalayan range in India with an Antitussive dose of 1-3 g.²⁸

Kantakari

The plant Kantakari (*Solanum xanthocarpum*) is a spiny herb bearing yellow fruits with green streaks. Microscopic section of the fruit displays epidermal cells with multicellular trichomes, parenchyma, vascular bundles, and calcium oxalate crystals. It is prevalent in dry tropical scrub and open woodland habitats in India. Antitussive activity of kantakari is administered in dose ranges of 3-6 g through traditional formulations.²⁹

Ethnopharmacology Studies

The polyherbal formulation composed of kantakari, pushkar root, and bharangi presents a scientifically rational and therapeutically synergistic approach by black pepper, ginger and honey for the management of cough and respiratory disorders by targeting multiple pathological pathways simultaneously. Amla rich in vitamin C and potent polyphenols, strengthening respiratory immunity and protecting airway epithelium also mitigates oxidative stress and modulates inflammatory mediators, thereby Black pepper, enriched with piperine, enhances bronchodilation through β -adrenergic stimulation, improves drug bioavailability of expectorants. Ginger, containing gingerols and shogaols, inhibits cyclooxygenase and lipoxygenase pathways, while also inducing smooth muscle relaxation and suppressing the cough reflex exerts significant anti-inflammatory action. Honey acts as a natural demulcent, forming a soothing protective barrier over irritated mucosa, alongside its antimicrobial and immunomodulatory properties. Bharangi promotes bronchodilation and mucus clearance through antihistaminic activity, reducing allergic responses and bronchial inflammation. Pushkar root, rich in sesquiterpene lactones, inhibits NF- κ B signaling pathways, thereby exerting potent anti-inflammatory and bronchodilatory effects, along with antimicrobial action. Kantakari alleviates bronchial irritation, reduces cough sensitivity, and enhances expectoration by steroidal alkaloids. Collectively, this formulation exhibits a powerful synergistic interplay, integrating bronchodilatory, anti-inflammatory, antitussive, expectorant, antimicrobial, and bioavailability-enhancing mechanisms, ultimately offering a comprehensive and effective natural therapeutic strategy for respiratory health. The phytochemical composition and pharmacological activities of selected herbal drugs, as described and evaluated in the Table 1.

Table 1. Ethnopharmacological Evaluation of Selected Herbal Drugs Showing Phytoconstituents and Pharmacological Activities

S.No	Herbal Drug	Phytoconstituents	Pharmacological Activity	Reference
1.	Amla	Vitamin A, B&C, Flavonoids, tannins, polyphenols	Antioxidant, anti-inflammatory, and immunomodulatory	30,31
2.	Black pepper	Piperine, volatile oil, alkaloid, lignans	Antimicrobial, anti-inflammatory, bronchodilator, expectorant	32,33
3.	Ginger	Gingerols, shogaols, zingerone, paradols and essential oil	Antioxidant, anti-inflammatory, anti-tussive, bronchodilator, and expectorant	34,35
4.	Honey	Glucose, fructose, phenolic acid and flavonoids	Demulcent, cough suppressant, Antioxidant, Antimicrobial, and anti-inflammatory .	26

5.	Bharangi	Flavonoids, sterols glycosides, and phenolic compounds	anti-inflammatory, antiallergic, anti-tussive, bronchodilator and expectorants	36
6.	Pushpakar root	Sesquiterpene lactones, essential oil and inulin	anti-inflammatory, anti-microbial anti-tussive, bronchodilator and expectorants	37,38
7.	Kantakari	Steroidal alkaloids, saponins, flavonoids and tannins	anti-inflammatory, anti-microbial anti-tussive, bronchodilator and expectorants	39,40

Synergistic Action

The polyherbal combination of Amla, black pepper, ginger, honey, Bharangi, Pushkarmool, and Kantakari exhibits significant synergistic activity by acting on multiple pharmacological targets involved in cough and respiratory disorders. Black pepper contains piperine which plays a crucial role as a bioenhancer, increasing the bioavailability and therapeutic efficacy of co-administered phytoconstituents such as flavonoids and phenolics from Amla, Bharangi, and Kantakari by inhibiting hepatic and intestinal drug-metabolizing enzymes. Ginger, which suppresses inflammatory pathways and directly inhibits the cough reflex at the central level, enhances the antitussive effect through its active constituents, gingerols and shogaols, when combined with other herbs.⁴¹ Pushkar root and Bharangi further potentiate bronchodilation and anti-inflammatory responses, while Kantakari complements these effects by reducing bronchial hyperresponsiveness and facilitating mucus clearance. Honey provides rapid symptomatic relief and supports the action of other

ingredients, is also enhancing the overall formulation by acting as a demulcent and improving mucosal absorption. Additionally, the combination of Amla, ginger, and other phytoconstituents reduces oxidative stress, which is a key factor in chronic respiratory inflammation. Studies on herbal cough formulations confirm that such combinations provide enhanced expectorant, antitussive, and bronchodilator effects compared to individual components due to their multi-target and complementary mechanisms. Thus, the formulation exhibits true pharmacological synergy by anti-inflammatory action, cough suppression, and mucus clearance, resulting in improved therapeutic outcome.^{42,43}

Methodology

Ingredients and their Function

The following medicinal plants are incorporated in the preparation of a polyherbal syrup formulated to produce expectorant and cough-suppressing effects.⁴⁴ The Formulation details of the polyherbal cough syrup are presented in Table 2.

Table 2. Composition of Polyherbal Cough Syrup with Functional Activities of Each Ingredient

S.No	Ingredients	Activity
1.	Amla	Antioxidants, immunomodulator
2.	Black pepper	Anti-tussive, expectorant.
3.	Ginger	Anti-inflammatory, Anti-tussive
4.	Honey	Sweetener
5.	Bharangi	Anti-inflammatory, antiasthmatic.
6.	Pushpakar root	Expectorant, bronchodilators
7.	Kantakari	Expectorant, bronchodilators
8.	Methyl paraben	Preservatives
9.	Propyl paraben	Preservatives
10.	water	Solvent

Preparation of Plant Material

The first step in preparing plant material is to collect the right parts of the plant at the right time and right condition in its growth. Remove dirt and other impurities, wash the collected material with water for 2 to 5 minutes, then

allow it to dry⁴⁵. The drying process help to prevent the contamination and degradation of plant materials. Shade drying is commonly used. Shade drying done to dry the compound at 25–30°C for 5–10 days or by using a hot air oven at 40–50°C for 24–48 hours^{46,47}. After the drying

process is completed, the material is ground into powder for 5 to 15 minutes and then passed through a 40 to 60 mesh sieve to make uniformity of the all-particles size. It should be packed in airtight container and keep at 20–25°C in a dry place then away from light and moisture.⁴⁸

Preformulation Studies

Organoleptic Evaluation

A small quantity of powdered drug is observed and its colour, odour, and taste are noted.

Determination of pH

The formulation/extract is checked for pH to comply with the site of administration. The pH is generally determined by the triple point method. After calibration, the end of the pH meter is dipped into the sample solution.

Loss on drying

A predetermined quantity is added in a clean and dried petri dish. It is placed for drying in a hot air oven for a definite period. Then the dry sample is weighed.

Value of Ash

A predetermined amount of the dried sample is placed in a crucible. The sample is incinerated in a muffle furnace. After the incineration, the weight of the resulting ash is recorded.

Value of Extraction

predetermined amount of powdered drug, macerate in 100 ml of solvent (water or alcohol) for definite period with occasional shaking, filter, evaporate the filtrate, and record the residue weight.⁴⁹⁻⁵¹

Compatibility Studies

A small quantity of herbal extract is blended with excipients and set aside for 24–48 hours. The preparation is closely monitored for any visible alterations in colour, odour, or signs of precipitation. All observations are systematically documented.^{52,53}

Extraction Method

Maceration

Maceration is a simple and widely used method for getting active ingredients out of medicinal plants. In this method, the drug is coarsely ground and put into a suitable solvent at room temperature for a set amount of time. This lets the soluble phytochemicals slowly diffuse into the solvent. This method works best for separating polar and heat-sensitive compounds, such as alkaloids, flavonoids, glycosides, tannins, and volatile oils.^{54,55}

Decoction

In this method, a specific amount of dried plant matter is taken and cut into small pieces or ground into a rough powder. Then, in the right amount, usually one part drug to ten parts water, it is mixed with water. The mixture is heated over a low flame and boiled for 15 to 30 minutes so that the active ingredients can get into the water. It is stirred every so often while it boils. The mixture is set aside to cool down after being heated. Then, a clean cloth or filter paper is used to get rid of the solid particles. The liquid that comes out after filtering is called the decoction.^{56,57}

Formulation of Polyherbal Syrups

The final syrup, the water extracts of all the chosen herbs were mixed together in the right amounts. Honey was added to make it taste better and calm down. Preservatives like methyl paraben and propyl paraben.^{58,59} To make sure that the mixture was even, it was stirred well in a clean environment. When needed, citric acid was used to change the pH of the formulation to about 6.0–6.5. After filtering out any suspended particles, the syrup was put into sterilized amber-colored bottles for storage.⁶¹⁻⁶³

Evaluation of a polyherbal syrup

Evaluation of a polyherbal syrup involves assessing its quality, safety, stability, and effectiveness. It includes examination of organoleptic properties like colour, smell, taste, and clarity, as well as physicochemical properties like pH, viscosity, and solubility. Phytochemical screening shows that there are active ingredients, and microbial tests make sure that the product is safe according to World Health Organization standards.^{64,65} The International Council for Harmonisation does stability studies to see if anything changes while the product is being stored. We also check the formulation for antitussive activity, how it settles, how much sugar it has, and how well it fits in with the packaging to make sure it is of good quality and works as a medicine.^{66,67}

Conclusion

This review explains the use of traditional plants in the treatment of antitussive activity via polyherbal formulations. This ethnopharmacological approach helps in inducing immunity to microbial infections and communicable diseases in which cough is a primary symptom. Proper *in-vitro* and *in-vivo* studies on antitussive activity can help in effective validation of the therapeutic activity of such formulations reducing the onset of cough related ailments and communicable diseases.

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