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Review Article

Search for the Natural Remedies for the Treatment of Dry Cough

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Abstract

Cough, also known as tussis, is a normal physiological response to any intrusion in the airway. However, this protective mechanism can turn into a nuisance if it becomes persistent, significantly impacting the social, physical, and psychological performance of a person. Standard antitussive agents like dextromethorphan (DXM), codeine, and gabapentin produce various side effects, and in some cases, cough relapse occurs as soon as drug doses are reduced. In search of better alternatives, this article delves into plant-based antitussive agents, studied in-vivo in various cough models. The cough models used in these studies include sulfur dioxide (SO_2), citric acid, ammonia, acetic acid, and capsaicin-induced models. The plant-sourced agents, included in this review article, are not only effective against dry cough but also have better safety profiles and lower addiction potential as compared to the mainstream options. The review article cites the examples of *Caesalpinia pulcherrima,* arabinogalactan extracted from the roots of *Withania somnifera,* vitexin from *Jatropha mutabilis, Napoleonaea vogelii, Rosa damascene* and *Hedera helix,* which were not only potent antitussives but were also had better safety and performance profile than standard drugs like codeine. By investing in these phytochemicals, exhibiting promising cough-suppression abilities, better, safer, and cheaper antitussive agents can be produced.

Keywords: Natural compounds, medicinal plants, cough, dry cough, cough suppressant, herbal medicine, anti-tussive

1. Introduction

Cough is one of the most common complaints patients seek medical attention for, in an outpatient setting (Mahashur 2015). A cough reflex is a physiological defense mechanism, it may resolve as soon as the airways are cleared but a persistent cough can impair the daily activities of a person, this is where a medical intervention should be considered (Padma 2013, Simpson and Amin 2006). The cough reflex may serve as a symptom for a wide range of diseases and a definitive treatment depends on identifying the cause and diagnosis. The cough reflex is divided into two categories; one is acute or short-lived, associated with upper respiratory tract infections, and gets resolved in 2-3 weeks, while the other is called chronic/persistent cough which lasts longer than eight weeks. Chronic cough can severely impact the quality of life by disturbance of sleep, exhaustion, urinary stress incontinence, cough syncope, and work absenteeism, culminating in severe physiological and psychological distress (Rai 2013). In more severe cases, persistent cough can also cause rib fractures, pneumothorax, pneumomediastinum, and subcutaneous emphysema. However, an accurate and early diagnosis of cough is the key to successful management. Idiopathic cough is rare and is often misdiagnosed, especially when the cause of the cough is extra-pulmonary. Asthma, gastric reflux, and rhinitis are common causes from three different anatomical areas and the realms of different specialists (Iyer and Joshi 2013).

Antitussives are the medical agents that are used for symptomatic relief of dry and non-productive cough. Various combinations and classes of these agents are available, which come with their own set of risks and benefits. As the world pivots toward more organic solutions, antitussives extracted from plant-based sources can prove to be equally beneficial and may potentially reduce the side effects that are associated with allopathic/western cough-suppressing agents.

2. Epidemiology and Prevalence

Chronic cough affects around 10% of adults globally. However, the prevalence of chronic cough is higher in Europe, America, and Australia (10–20%) than in Asia (<5%) (Song et al. 2015, Yang, Chung, and Huang 2023). The general population of Copenhagen, Denmark, showed the prevalence of chronic cough to be 4%, 3% in never-smokers, 4% in former smokers, and 8% in current smokers (Çolak et al. 2017). An Australian study found that the prevalence of chronic cough, in the Aussie subjects was 10% (Suresh et al. 2023). While in China, the prevalence of chronic cough is found to be 6.2% in adults, through meta-analysis (Liang et al. 2022). In India, the prevalence of chronic cough was 2%, as found in a study involving 3,465 subjects in an urban area of East Delhi. In a similar study, conducted in South India, the prevalence of cough in 4,333 adults (age > 30 years) was 2.5%. (Mahesh et al. 2011). Another study conducted in India, over 3 months with 500 registered physicians, reported that 11-20% of the patients presented with dry cough, while more than 30% of their patients had a chronic cough (Pore, Biswas, and Das 2016).

In Pakistan, a study conducted to probe into the health problems of in farmers Khyber Pakhtunkhwa found that of the 206 subjects 52.43% (n=108) suffered from dry cough (Ishtiaq et al. 2023). Similarly, a cross-sectional study was conducted in Islamabad, which aimed at finding the prevalence and characteristics of chronic cough. It found that the main causes of chronic cough were asthma, angiotensin-converting enzyme inhibitors (ACEI) induced cough, allergic rhinitis, gastroesophageal reflux disease, interstitial lung disease, bronchial hyper-reactivity, and others. Out of 236 chronic cough patients who attended, 111(47%) had a chronic dry cough, with asthma being the major pathological factor (Toori and Chaudhry 2020). Another study found ACEI-induced cough has been reported to emerge in 5-20% of ACEi-treated individuals, particularly in people of East Asian descent. In the Pakistani cohort, the incidence of cough with enalapril was 20%, 16.6% with captopril, 15% with perindopril, and 10% with lisinopril and ramipril. The study also listed genetic polymorphisms that predispose a population to dry cough, following ACEI therapy initiation (Sheikh, Memon, and Sahar 2022).

3. Pathophysiology of Dry Cough

As previously mentioned, cough is a protective reflex or a part of the body's defense system. It is involved in the clearance of particulates and secretions from the airways and protects from aspiration of foreign materials as well as pathogens. In some conditions, this protective mechanism may become excessive and nonproductive, potentially harming the airway mucosa. These contrasting results of coughing can be attributed to the parallel afferent pathways regulating it (Polverino et al. 2012). The cough reflex arc is constituted of an afferent pathway, a central pathway (cough center), and an efferent pathway.

The process of producing a cough response begins with the stimulation of an afferent pathway after irritation of cough receptors located in the pulmonary, auricular, pharyngeal, superior laryngeal, gastric, cardiac, and esophageal branches from the diaphragm. Subsequently, afferent impulses produced by the sensory nerve fibers (vagus nerve branches) go to the 'cough center' located in the medulla, diffusely. A central coordinating region for coughing is located in the upper brain stem and pons. The cough center is responsible for generating an efferent signal. The efferent signals travel through the vagus, phrenic, and spinal motor nerves to the expiratory musculature diaphragm (abdominal wall and

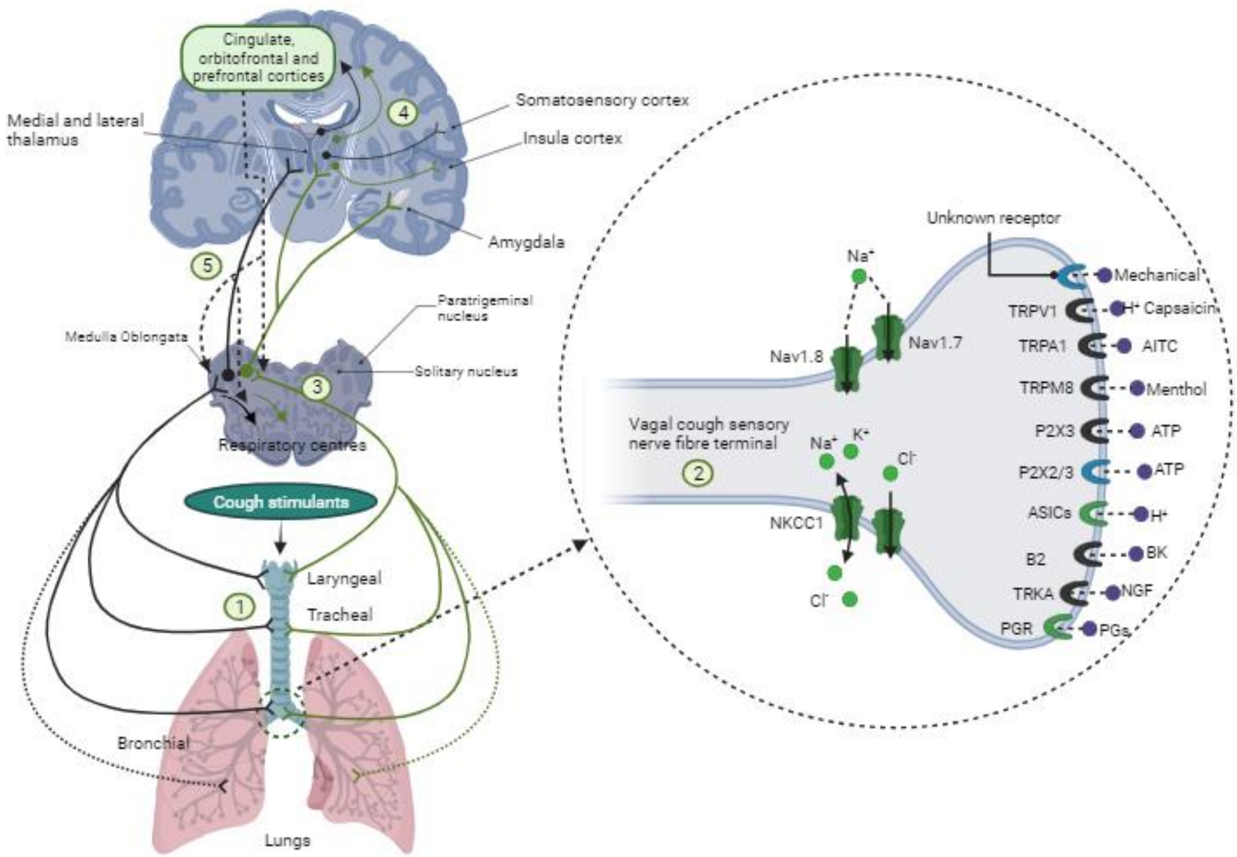

Figure 1. This figure shows the general pathophysiology of the cough reflex. Allyl isothiocyanate (AITC); acid-sensing ion channel (ASICs) subtypes; bradykinin type 2 receptor (B2); chloride channel subtypes (CLC); protons/acid (H^{+}); voltage-gated sodium channel (Nav) subtypes; nerve growth factor (NGF); sodium (Na^{+}) potassium (K^{+}) chloride (Cl^{-}) co-transporter (NKCC1); purinergic receptor (P2X) subtypes; prostaglandin (PG); prostaglandin receptor (PGR); tyrosine receptor kinase A (TrkA); transient receptor potential (TRP) cation channel.

muscles), producing cough (Polverino et al. 2012, Lee et al. 2021). However, an increased sensitivity of the cough reflex can be observed in patients with dry cough (Padma 2013). The cough reflex can be triggered by either mechanical stimulation or chemical stimulation, such as sulfur dioxide, ammonia, citric acid, and capsaicin (Saadat, Shakeri, and Boskabady 2018).

As shown in Figure 1, vagal sensory neurons that are involved in cough innervate the larynx, trachea, main bronchi, and possibly, the lung parenchyma (black and green dashed lines). Vagal Aδ fibers (whose cell bodies reside in the nodose ganglia) are activated by mechanical stimuli (such as inhaled particulate matter, mucus, and aspirated gastric contents) and protons. Whereas vagal C- C-fibers (whose cell bodies reside in the jugular ganglia) are activated by irritant chemicals and inflammatory mediators. **(2)** Vagal fibers involved in cough express several ion channels and receptors needed for the transduction of diverse sensory stimuli and the formation, conduction, and regulation of action potentials, and **(3)** project to brainstem nuclei to coordinate cough motor patterning. **(4)** Distinct networks in the higher brain are involved in the behavioral regulation of cough, encoding of the urge to cough, and cognitive and affective processing. **(5)** Central mechanisms allow for volitional and cognitive modulation of cough through top-down regulation of brainstem processing (black dashed lines).

4. Conventional Treatment

When the cough interferes with the patient's daily activities, symptomatic relief must be considered. Antitussives are used for effective symptomatic relief of dry or non-productive cough, which are available as combinations of codeine or dextromethorphan (DXM) with antihistamines, decongestants, and expectorants. The sedative effect produced by these substances is also important if the cough is disturbing the sleep cycle of a patient (Padma 2013).

Common used antitussive agents in clinical practice include centrally acting agents like codeine, pholcodine, DXM, methadone, and morphine. These medications work by directly affecting the cough center in the brain, reducing the nerve impulse discharges to the muscles responsible for producing cough. On the other hand, peripherally acting antitussives function by inhibiting the responsiveness of the afferent or efferent nerves involved in the cough reflex. Peripherally acting agents are categorized as demulcents, local anesthetics (lidocaine, benzocaine, hexylcaine hydrochloride, and tetracaine), humidifying aerosols (Mahashur 2015), and gabapentin also significantly improved subjective cough measures and objective cough frequency in patients with chronic refractory cough (Chung et al. 2022).

5. Challenges with Conventional Treatment

Chronic cough is often difficult to treat because it doesn't always respond well to treatments targeting the underlying cause (Grabczak et al. 2020). Ongoing efforts aim to develop more effective and safe antitussive (cough-suppressing) medications.

A study was conducted in groups of patients with chronic cough. The codeine-receiving group experienced drowsiness, constipation, and headaches more than the levodropropizine group (Lee and Lee 2022). In addition to the side effects, the opioid epidemic is another global health concern, the ripple effects of which are impacting other socioeconomic indicators of societies. Misuse and dependency on codeine-containing products are also on the rise, even among healthcare professionals (Akande-Sholabi et al. 2019).

Moreover, due to easy access, euphoric high, and hallucinogenic effects at larger doses, DXM often attracts drug abusers. More than 50 deaths were reported for the first time in Pakistan due to cough syrups, containing DXM. All those who died had a history of drug abuse and their toxicological analysis showed that the deceased had purposefully ingested large (toxic) doses of DXM for recreational purposes. Besides DXM, chlorpheniramine (antiallergy, antitussive) abuse was also detected in the same toxicology report (Shafi et al. 2016, Chyka et al. 2007).

In addition to this, codeine and DXM can significantly impact liver and kidney function and histology, as observed in a study involving rats. All doses of codeine and DXM significantly raised the ALT levels ($p < 0.05$). Similarly, statistically significant alterations were seen for the kidney function parameters. Notably, all doses of DXM caused significant elevations in the levels of urea ($p<0.05$). The histopathological evaluations also indicated slight changes in the architecture of the liver, kidney, and brain tissues. These drugs may potentially induce hepatic and renal injuries (Kayode, Kayode, and Oridota 2021)

About the use of neuromodulators, like gabapentin, for refractory chronic cough (RCC) management a study found that despite the efficacy of these agents, relapse was more common upon withdrawal or reduction of dosage. The study emphasized the dire need for developing novel medication for RCC management (Zhang et al. 2023).

6. Remedies from Medicinal Plants and Studies in Animal Models of Cough

Literature is replete with studies showing promising activities against several common diseases (Hussain et al. 2010, Imran et al. 2012, Al Mughairbi et al. 2021). Phytopharmacology has the potential to transform the antitussive drug landscape. The plant-derived antitussive can not only produce cough relief that is comparable to codeine or DXM but also has relatively safer pharmacological profiles. This article includes many examples of plant-based extracts with antitussive properties that have been tested in various cough models in animals, like rats, mice, and guinea pigs.

7. Sulfur Dioxide Induced Cough Model

SO_2 is an inhalable air pollutant, that generally induces cough by irritating the airways. In guinea pigs, there is a relatively enhanced nasal and lower airway sensitivity, similar to humans regarding histamine-driven immunoglobulin (Ig)E responses. Mice also exhibit airway inflammation and airway hyper-responsiveness in response to SO_2 exposure. Interestingly, SO_2 exposure in rats leads to a significant rise in mRNA and protein levels of these asthma-related genes(Reno, Brooks, and Ameredes 2015). SO2-induced cough model has been in use for some time for testing antitussive drugs in animals. In a study, SO_2 was administered through aerosol cans with a dosage nozzle. The test animals were exposed to this sulfur dioxide aerosol for a specified time. Coughing frequency was observed for a few minutes after the exposure (Karttunen, Koskiniemi, and Airaksinen 1982).

7.1. *Adhatoda vasica*

The antitussive action of *A. vasica* (Acanthaceae) against SO_2-induced cough was evaluated by the method described by (Miyagoshi, Amagaya, and Ogihara 1986). After ethanolic extraction from *A. vasica* leaves, it was administered to SO_2-impacted mice at 200mg/kg dose, orally. The extract showed a significant cough-suppression effect at the level of $p<0.01$. Cough reflex inhibition was 43.02%, at 200mg/kg dose of *A. vasica,* as compared to codeine sulfate (20 mg/kg) at 45.73% ($p<0.001$) at 60 minutes of the experiment. This provided pharmacological credibility to the folkloric claim of antitussive effects of *A. vasica* (Jahan and Siddiqui 2012).

7.1. *Glycyrrhiza glabra*

The ethanol extract from the roots of *Glycyrrhiza glabra,* from the Fabaceae family, was investigated for antitussive properties by (Shitole and Pawar 2019). The effect of the granules of *Glycyrrhiza glabra* extract on SO_2 gas-induced cough showed statistically significant effects ($p<0.01$) in inhibiting the cough reflex at a dose of 200 mg/kg body weight, in comparison with the control group. The plant-based antitussive preparation showed inhibition of cough on treatment comparable to that of codeine sulfate (dose: 20mg/kg, 41.17%, and 47.13%, respectively, at the 60-minute mark).

7.2. *Caesalpinia pulcherrima*

A study aimed at evaluating *C. pulcherrima* (Fabaceae) potential against cough by using an ethanol extract from the aerial parts of the plant. After the SO_2 cough induction method was applied to rats, then they were divided into four groups, and all drugs were administered orally. Group I served as control (on distilled water), group II as standard, while groups III and IV received 200 and 400 mg/kg *C. pulcherrima* extract. The percentage inhibition of cough by codeine (standard drug) was 97.5% at the 60-minute mark, while 200mg/kg extract showed 97.65% and 400mg/kg exhibited 98.35% inhibition in cough reflex, respectively, after 60 minutes. The study not only consolidated the safety profile of the extract but also found it to be a more potent antitussive agent (at 400mg/kg) as compared to codeine(Gilani et al. 2021).

7.3. *Celosia argentea*

In a study, concentrated and dried methanol extract granules from the leaves of *Celosia argentea,* of the Amaranthaceae family were prepared. To test the antitussive qualities of this extract an induced cough model in mice was used, under the guidelines provided by (Miyagoshi, Amagaya, and Ogihara 1986). As a result, codeine sulfate (20mg/kg) showed maximum inhibition of 47.13% ($p<0.01$) after 60 minutes of the experiment, whereas, The test group of mice showed 41.17%, inhibition of dry cough on treatment with *C. argentea* granules (200mg/kg) after the same period, at the level of $p<0.01$(Jadhav et al. 2022).

7.4. *Malva parviflora*

In addition to being used as an alternative food source, *Malva parviflora* (family: Malvaceae) possesses some anticough properties as well (Altyar et al. 2022). conducted a study to test the antitussive potential of *M. parviflora* by preparing a mucilage extract from the leaves (MLM) and unripe fruit (MFM) of this plant. Post-SO_2 gas cough induction, codeine (10mg/kg) was administered in one group of rats, which lowered the cough frequency from 127.6 to 53.8 (57.8% inhibition). However, MLM oral administration (500mg/kg) significantly decreased the number of coughs from 127.4 to 66.2 (47.99 % inhibition). On the other hand, the least antitussive activity was observed in animals treated with MFM (500mg/kg) which decreased the cough frequency from 133 to 91.66 with (31.37% inhibition). The study concluded that there was a non-significant difference in the percentage inhibition of cough in MLM-treated rats when compared with the standard drug, and also confirmed the demulcent action of the mucilage of *M. parviflora* empirically.

8. Citric Acid Induced Cough Model

A study showed that micro-aspiration of acid into the lower airway elicits cough and bronchoconstriction through airway acidification, which results in the activation of capsaicin-sensitive primary sensory neurons, which contain neuropeptides as neurokinin A (NKA), producing major signs of inflammation (neurogenic inflammation) employing activation of NK1 and NK2 receptors, which are involved with citric acid-induced bronchoconstriction in the guinea pig (Ricciardolo 2001). Similarly, in another investigation by(Tanaka and Maruyama 2005), citric acid was administered through inhalation, and microinjection into the larynx of guinea pigs. Upon inhalation of citric acid, a cough reflex was induced in a dose-dependent manner, and coughs were reduced upon capsaicin pretreatment. This suggests that citric acid induces coughs by activating capsaicin-sensitive C-fibers (as suggested by (Yagi et al. 2001). On the other hand, citric acid microinjection induced three-fold larger responses than inhalation and capsaicin pretreatment did not abate this reaction, suggesting that citric acid stimulates afferent fibers other than C-fibers in the larynx, possibly Aδ-fibers (cough receptors) as identified by (Canning et al. 2004). The study concluded that this model can be used for analyzing various coughs and evaluation of antitussive drugs.

8.1. *Withania somnifera*

A study aimed to evaluate the antitussive activity of arabinogalactan, extracted from the roots of *Withania somnifera* (Solanaceae), in addition to the role of the opioid pathway in this action, in healthy adult guinea pigs. Cough was induced, in the guinea pigs, by an aerosol of citric acid, and the polysaccharide extract was given orally at a dose of 50 mg/kg. The results indicated that arabinogalactan suppressed the cough reflex; moreover, the intensity of suppression was comparable with that of codeine (reference drug). Although the study failed to confirm the presence of a bronchodilatory effect by the polysaccharide, the *W. somnifera* root-extract was confirmed to have a distinct antitussive activity, as it may potentially involve the mu-opioid receptor pathways (Nosalova et al. 2013).

8.2. *Sterculia setigera, Aframomum melegueta,* and *Citrus aurantifolia*

An investigation into the antitussive effect produced by *Sterculia setigera* (Sterculiaceae), *Aframomum melegueta* (Zingiberaceae), and *Citrus aurantifolia* (Rutaceae) was done. A decoction from the leaves, seeds, and leaves and fruits of these plants was prepared, respectively. At 3000 mg/kg, *the A. melegueta* and *C. aurantifolia* mixture significantly outperforms New Codion ® (codeine), achieving a 73.70% inhibition rate (dose-dependent antitussive activity) compared to New Codion's (codeine) 63.20%. On the other hand, *S. setigera's* antitussive effect at 3000 mg/kg was 50.70%. The use of these phyto-extracts as antitussive is justified by this study. Moreover, no toxic effect or side effect was observed post-administration of the mixtures, establishing their safety profile (Aïkpe et al. 2020).

8.3. *Jatropha mutabilis*

A study aimed at isolating and evaluating the antitussive activity of vitexin from *Jatropha mutabilis,* from the Euphorbiaceae family. For vitexin isolation, the pulverized leaves of *J. mutabilis* were first macerated in ethanol, later this solution was subjected to hydroalcoholic extraction (water+ methanol). This extract was then subjected to liquid-liquid partitioning using solvents of varying polarities (hexane, chloroform, and ethyl acetate). During the concentration of the ethyl acetate phase, a yellow precipitate formed, which was later purified through recrystallization with methanol, resulting in the isolation of vitexin. Additionally, vitexin and β-cyclodextrin (β-CD) IC (Inclusive complex) were prepared (1:1 molar ratio), to improve the solubility of vitexin. To test the antitussive effects of vitexin and vitexin complex, a cough reflex was induced in mice by exposing them to a nebulized solution of citric acid, and counting the number of coughs before the treatment. After 23 hours and 30 min of the initial exposure to citric acid, mice were treated orally with codeine (30 mg/kg), vitexin suspended in distilled water (0.2mg/kg, 1mg/kg or 5mg/kg), vitexin/β-CD IC (dose of vitexin at 0.2mg/kg, 1mg/kg or 5 mg/kg in the complex), β-CD (vehicle of complexed vitexin) or distilled water (free vitexin vehicle) and, after 30 min, the animals were subjected to secondary exposure of citric acid, number of coughs produced were counted and compared to the previous exposure. The results showed that vitexin doses were 0.2 mg/kg, 1 mg/kg, and 5 mg/kg, while vitexin/β-CD complex doses 1 mg/kg and 5 mg/kg produced a potent cough-suppression effect. Moreover, vitexin showed efficacy at a dose that was 30 times lower than the dose of codeine, making its antitussive effect superior to that produced by codeine (Costa et al. 2020).

8.4. *Cannabis sativa*

A study used root samples of *C. sativa*, from the family Cannabaceae, to test its antitussive properties. An aqueous extract from the roots of *C. sativa* was prepared, with subsequent lyophilization, to maintain the material stability. Using liquid-chromatography-mass-spectrometry, 5 molecules in C. sativa roots were identified: p-coumaroyltyramine, tetrahydrocannabinol-C4, feruoiltyramine, anhydrocanabisativine, and cannabisativine. After this, the extract (at doses of 12.5, 25, or 50 mg/kg) was tested in animal models of citric acid-induced cough. The results showed *C. sativa* root extract carried the potential to treat cough, in a dose-dependent manner. The antitussive effects were observed even after intense secondary metabolites' transformation, with variation in potency. The results prove that the traditional use of *C. sativa,* as an antitussive agent, is empirically justified (Menezes et al. 2021).

8.5. *Juglans regia*

The antitussive *Juglans regia* (Juglandaceae) septum extract (WSE) was investigated using the citric acid aerosol-induced cough model. The extraction was made by using acetone solvent. In one group of rats, codeine phosphate was given at a dose of 3 mg/kg/ day, which significantly reduced the number of coughs to an average of 15.4 and increased latency to 144 seconds, compared to the untreated control group ($p < 0.01$), with minimal nasal irritation and bleeding. Interestingly, WSE showed dose-dependent antitussive activity, comparable to that of codeine. In the group receiving a dose of 10 mL/kg/ day (equivalent to 134 mg GAE/kg body weight per day), WSE significantly reduced cough frequency, with an average of 10.3 coughs in 8 minutes, and extended the latency to 81 seconds. In the WSE 1:2 group, which received a lower dose of 67 mg GAE/kg body weight per day, there was a 20% reduction in cough frequency, and the latency increased to 56 seconds. Notably, animals in both WSE-treated groups did not display any sign of nasal irritation or bleeding (Fizeșan et al. 2021).

Table 1: Antitussive Plant Extracts Studies in Cough Models

Plant Name	Family	Part used	Crude Extract/Fraction/Compound	Mechanism	Reference
Erigeron canadensis	Asteraceae	Flower	Polyphenolic polysaccharide-protein	Reduces citric acid-induced cough	(Šutovská et al. 2022)
***Marsilea minuta* L.**	Marsileaceae	Whole plant	Methanol, ethyl acetate, and petroleum ether fractions	Reduces NH_3 and SO_2-induced cough	(Chakraborty et al. 2013)
Lycopus europaeus	Lamiaceae	Whole plant	Methanolic extract	Reduces ammonia and SO_2-induced cough	(Aziz et al. 2013)
Euphobia hirta* and *Lactuca virosa	Euphorbiaceae, Asteraceae	Whole plant, Leaves	Aqueous extract	Reduces citric acid & NH_3-induced cough	(Uwaya, Bello, and Aikpitanyi 2023)
Glycyrrhiza glabra	Fabaceae	Roots	Granules made from ethanol extract	Reduces SO_2-induced cough	(Shitole and Pawar 2019)
Adhatoda schimperiana	Acanthaceae	Leaves	80% methanol extract	Reduces NH_3-induced cough	(Petros 2020)
Adhatoda vasica	Acanthaceae	Leaves	Ethanol extract	Reduces and SO_2-induced cough	(Jahan and Siddiqui 2012)
Caesalpinia pulcherrima	Fabaceae	Aerial parts	Ethanol extract	Reduces SO_2-induced cough	(Gilani et al. 2021)
Cannabis sativa	Cannabaceae	Roots	p-coumaroyltyramine, tetrahydrocannabinol-C4, feruoiltyramine, anhydrocanabisativine, and cannabisativine.	Reduces citric acid-induced cough	(Menezes et al. 2021)
Cordia myxa	Boraginaceae	Fruit	Nano and bulk hydroalcoholic maceration exrtact	Reduces NH_3-induced cough	(Salimimoghadam et al. 2019)
Reineckia carnea	Convallariaceae	Aerial parts	Aqueous extract & 60% ethanol extract	Reduces NH_3-induced cough	(Han et al. 2010)
Withania somnifera	Solanaceae	roots	/Arabinogalactans (polysaccharides)	Reduces citric acid-induced cough	(Nosálová et al. 2015)
Rosa damascene, Hedera helix	Rosaceae, Araliaceae	Flower, leaves	Distilled rosewater (petal extract) / polyphenolic compounds (flavonoids)	Reduces NH_3 and SO_2-induced cough	(Abidi et al. 2021)
Juglans regia	Juglandaceae	Kernel (Walnut septum)	Walnut septum extract	Reduces citric acid-induced cough	(Fizeșan et al. 2021)

Ocimum sanctum	Lamiaceae	leaf and root	Aqueous extract	Reduces SO_2-induced cough	(Billah et al. 2021)
Malva parviflora	Malvaceae	Leaves and unripe fruit	Mucilage extract	Reduces SO_2-induced cough	(Altyar et al. 2022)
Celosia argentea	Amaranthaceae	Leaves	Methanol extract/ steroids, saponin, alkaloids, flavonoids, and glycosides	Reduces NH_3 and SO_2-induced cough	(Jadhav et al. 2022)
Chrysophyllum albidum	Sapotaceae	Leaves	Crude aqueous extract/ tannin, cardiac glycoside, saponin, flavonoid, and phenol	Reduces NH_3 and acetic acid-induced cough	(Agbaje and Nzeh 2021)
Cydonia Oblonga	Rosaceae	Seed	Aqueous extract / saponins	Reduces NH_3-induced cough	(Lataran et al. 2023)
Napoleonaea vogelii	Lecythidaceae	Leaves	Methanol extract/ tannins, alkaloids, anthraquinone, flavonoids, saponins,	Reduces NH_3 and citric acid-induced cough	(Adejayan et al. 2019)
Tagetes erecta	Asteraceae	Flower	Rutin extraction via maceration followed by ultra-sonication.	Reduces NH_3-induced cough	(Moravkar et al. 2023)
Sterculia setigera, Aframomum melegueta and Citrus aurantifolia	Sterculiaceae, Zingiberaceae, and Rutaceae	Leaves, seeds, and fruits	Aqueous extract prepared by decoction	Reduces citric acid-induced cough	(Aïkpe et al. 2020)
Jatropha mutabilis	Euphorbiaceae	Leaves	Ethanolic extract/ Vitexin	Reduces citric acid-induced cough	(Costa et al. 2020)
Dioscorea rotundata	Dioscoreaceae	Stem	n-hexane, ethyl acetate, and methanol extracts	Reduces citric acid-induced cough	(Ogbuanu et al. 2022)
Houttuynia cordata	Saururaceae	Leaves	Petroleum ether, benzene, chloroform, acetone, ethanol, and aqueous fractions	Reduces NH_3 and citric acid-induced cough	(Warjri and Das 2023)

8.6. *Erigeron canadensis*

A study was conducted to find the curative role of *Erigeron canadensis* (Asteraceae), particularly in cough and airway reactivity. In this study, the polyphenolic polysaccharide-protein complex was extracted from the flowering parts of *E. canadensis* by using a hot alkaline extraction method, followed by a multi-stage purification process. The antitussive activity, produced in a dose-dependent manner, was statistically significant, similar to that of codeine. The findings were confirmed by a decrease in the number of citric acid-induced coughs. With a decrease in specific airway resistance in conscious guinea pigs, the bronchodilator effect was also verified (Šutovská et al. 2022).

8.7. *Dioscorea rotundata*

In Oghe Traditional medical practice, *Dioscorea rotundata* (family: Dioscoreaceae) plant stem oral paste is used for controlling persistent cough and hiccups. To confirm the antitussive activity of *D. rotundata*, an in-vivo study, using guinea pigs was conducted. Tussis was induced in the test animals by using citric acid fumes. Three extracts were made from the stem of *D. rotundata* by using 1000 mL of n-hexane, ethyl acetate, and methanol. DXM (standard drug) dramatically reduces the number of coughs by 71.81%, while ethyl acetate extract inhibits cough reflex by 67.69%, 50.35%, 45.23%, and 24.21% at dosages of 100mg, 75mg, 50mg, and 25 mg. Notably, the n-hexane and methanol extracts of *D. rotundata,* at different concentrations, failed to show any noteworthy reduction in the number of coughs (Ogbuanu et al. 2022).

9. Ammonia-Induced Cough Model

Ammonia is highly irritating to the respiratory tract. Exposure to ammonia can lead to swelling and narrowing of the throat and bronchi, coughing, and accumulation of fluid in the lungs(Registry). Ammonium hydroxide (aqueous solution of ammonia) appears as a colorless aqueous solution and the concentration of ammonia ranges up to approximately 30%. Ammonium hydroxide also produces cough, sore throat, burning sensation, labored breathing, and shortness of breath upon inhalation (Information 2023). This principle is used in the ammonia-induced cough model for purposes like antitussive drug tests.

9.1. *Reineckia carnea*

A study aimed at evaluating the cough-suppression potential of *Reineckia carnea* (Convallariaceae). *R. carnea* is traditionally used as an antitussive agent in Chinese traditional medicine. The aqueous extract and four fractions of the aerial part of *R. carnea* were given orally to mice with cough, induced by ammonium hydroxide. The results showed that a 90% Ethanol fraction significantly increased the cough latent period and reduced the frequency of cough, at the dose of 0.372 g/kg ($p < 0.05$). 60% percent ethanol fraction also reduced the cough at 0.570 g/kg ($p < 0.05$). It was concluded that the 60% ethanol and 90% ethanol fractions were effective in reducing cough (Han et al. 2010).

9.2. *Cordia myxa*

An investigation to see the antitussive effects of *Cordia myxa* (Boraginaceae) used its fruit extract to study its effects in in-vivo settings. The researchers prepared a hydroalcoholic extract (bulk extract) and nanoparticles of the hydroalcoholic extract to compare their pharmacological activities and cough suppression efficacy. Ammonia-induced cough model was used to produce tussis in mice and then the positive control group was treated with DXM (10mg/kg, orally), whereas bulk extract and nanoparticle extract were given at the dose of 750mg/kg (intraperitoneal injection). The mean number of cough (pretreatment) was 86 which was reduced to 18.67 and 13.67 by nanoparticle extract and bulk extract, respectively, as compared to the control group ($P<0.0001$). However, both extracts were equally effective in reducing cough frequency ($P=0.377$). Notably, DXM only reduced the number of coughs to 20.17, which was also significant compared to the control group ($P<0.0001$) (Salimimoghadam et al. 2019).

9.3. *Adhatoda schimperiana*

Adhatoda schimperiana (Acanthaceae) has been used in Ethiopian traditional medicine as a cure for cough and bronchial asthma. An in-vivo investigation was carried out to test the validity of the antitussive effects of *A. schimperiana.* An 80% methanolic extract was prepared from the leaves of this plant. After exposing the mice to ammonium hydroxide (soaked cotton method), to induce cough reflex, the positive control group was treated with codeine phosphate (10 mg/kg/day), while *A. schimperiana* leaf extract was administered in 100mg, 200mg, and 400mg/kg/day, followed by secondary exposure to ammonium hydroxide (soaked cotton). The resulting data showed that codeine phosphate (10 mg/kg) significantly delayed the cough incubation period by 155.2%. The extract increased the latent period of cough in a dose-dependent manner, 400 mg/kg/day produced the most pronounced suppression by 92.9% ($P < 0.05$). Codeine phosphate (10 mg/kg) significantly suppressed the cough frequency by 74.0%. However, the extract at 400 mg/kg caused 57.5% inhibition of the cough frequency ($P < 0.05$) (Petros 2020).

9.4. *Cydonia Oblonga*

An in-vivo investigation was carried out into the antitussive effects of *Cydonia oblonga* of the Rosaceae family. Mucilage was extracted from the seeds of *C. oblonga* by using 3 methods: Single-step aqueous maceration, ultrasonic pretreatment followed by aqueous maceration, and microwave pretreatment followed by aqueous maceration. The antitussive effect of the quince seed mucilage at different concentrations of 100mg, 200mg, and 400 mg/kg was assessed. With an increasing dose (100mg to 400mg/kg) the cough latency period also got prolonged (from 13.7 seconds to 20.7 seconds). Whereas, the latency period produced by DXM (dose: 200mg/kg) was only 15.7 seconds. The group receiving a 400mg/kg dose of *C. oblonga* mucilage achieved the highest reduction in cough, with significant inhibition of 51.80%, and the latent cough period was prolonged by 121.4%. This is far superior to the effect produced by DXM where the number of coughs was reduced by 50.4%, and the incubation period was lengthened by only 67.8% (Lataran et al. 2023).

10. Multi-Model Studies

10.1. *Marsilea minuta*

The plant *Marsilea minuta* has a wide range of usage in India and Bangladesh. It is not only used as a vegetable but also has medical applications as well. A study aimed at evaluating the antitussive effects of M. minuta used methanol, ethyl acetate, and petroleum ether extracts of this plant against mice coughing, induced by using ammonia and SO_2 gas. Results indicated that pretreatment with codeine 30mg/kg, methanol, ethyl acetate, and petroleum ether extracts at a dose of 500mg/kg for 5 days produced cough inhibition at 69.1%, 55.8%, 56.8%, and 34.0% inhibition of SO_2-induced cough. While in the ammonia model, methanol extract inhibited cough reflex by 59.5% at 500mg/kg, and codeine at 30mg/kg produced 80.6% inhibition. The study found the methanol extract of *M. minuta* to be the most effective antitussive agent ***(***Chakraborty et al. 2013***).***

10.2. Lycopus europaeus

A study was conducted to find the antitussive cough activity of *Lycopus europaeus* (Lamiaceae), using ammonia- and SO_2-induced cough models, in mice. Methanolic extract from the *L. europaeus* plant was prepared and administered at 500mg/kg dose and exhibited significant antitussive activity (56.63%) in ammonium liquor-induced cough, while DXM showed 71.52% inhibition at 20mg/kg. Whereas, the extract showed cough inhibition (61.21%) in SO_2 gas-induced cough, as compared to codeine which produced inhibition of 76.43% at the dose of 20mg/kg (Aziz et al. 2013).

10.3. Napoleonaea vogelii

A study aimed at assessing the cough-suppression properties of *Napoleonaea vogelii* (Lecythidaceae), by using its leaf extract and evaluating it in citric acid and ammonia-induced cough model, in guinea pigs. The extract was administered in doses of 100, 200, or 400 mg/kg/day, and the positive control group was given 25 mg/kg of dihydrocodeine. Notably, the cough bouts were found to be decreased significantly ($P < 0.05$) in a dose-dependent way. In the citric acid model, doses of 200 mg/kg and 400 mg/kg significantly reduced the number of cough bouts ($P < 0.01$) and ($P < 0.001$), respectively. While in the ammonia model, the extract, at the dose of 400 mg/kg significantly reduced the number of cough bouts ($P < 0.001$). It was concluded that the extract was not only safe, owing to its high LD50 value (> 5000 mg/kg) but also a potent antitussive agent (Adejayan et al. 2019).

10.4. *Rosa damascene* and *Hedera helix*

To observe the synergistic antitussive effects of *Rosa damascene* (Rosaceae) and *Hedera helix* (Araliaceae), a study was carried out by using distillation method to prepare rosewater from *Rosa damascene* petals and combining it with ivy leaf (*Hedera helix*)extract, making a rosewater cough syrup in different compositions (5ml/70kg, 10ml/70kg, and 15ml/70kg). The different compositions were prepared as A1 (laboratory distillation, rose water), A2 (50% laboratory distilled rose water + 50% distilled water), A3 (commercial rose water), and A4 (50% commercial rose water + 50% distilled water). In the SO_2 model, the A1 formulation performed better than the standard DXM and diphenhydramine (10 ml/70kg), in suppressing cough ($p < 0.05$). In addition, 10ml/70kg formulation was tested in the ammonia-induced cough model and again A1 performed better than the standard drugs DXM and diphenhydramine (10 ml/70kg) (Abidi et al. 2021).

10.5. *Ocimum sanctum*

The roots and leaves of *O. sanctum* (Lamiaceae), also known as Holy Basil, have been used for their antitussive effects by many folk medical practitioners for quite some time. A study was conducted on mice with cough, using SO_2 gas-induced and capsaicin-induced cough models (the capsaicin-induced cough model works by activating TrpV1 receptors are key players in sensing acidosis, in mediating cough (Laird 2009)). In the investigation, various extracts were made from the leaves and roots of *O. sanctum.* After inducing cough, the individual doses of aqueous leaf and root extracts were tested at three different doses: 100 mg/kg, 200 mg/kg, and 400 mg/kg. Additionally, formulated extracts were prepared by mixing leaf and root extracts in different ratios, such as 50:150, 100:100, and 150:50 mg/kg. The antitussive output was compared with the standard drug codeine phosphate. In the SO_2-induced cough model, the leaf extract (400 mg/kg) was significantly effective in reducing the frequency of coughing, and this extract at 400mg/kg, when combined with codeine phosphate at 1 mg/kg, exhibited even more profound efficacy. In the same model, the root extract at 100 and 400mg/kg, combined with codeine phosphate at 1 mg/kg, showed its maximum efficacy at 60 minutes.

However, in the capsaicin-induced cough model, the standard treatment resulted in a significant reduction in coughing. The leaf extract (400mg/kg) alone was also effective in treating cough in this model. The leaf-dominant formulated extract, L: R (root) 150:50, when combined with codeine phosphate at 1 mg/kg, showed prominent potential and effectively reduced coughing (Billah et al. 2021).

10.6. *Chrysophyllum albidum*

Chrysophyllum albidum, from the family Sapotaceae, also known as the African star apple has been used for many ailments, including asthma and cough, in traditional African medicine. To evaluate its antitussive effects, a study tested its aqueous extract in mice. Two cough induction models were employed in this study, the ammonia- and acetic acid-induced cough model (acetic acid is thought to produce cough by lowering pH (Mochizuki et al. 1995, Wong, Matai, and Morice 1999)). *C. albidum* extract was administered at the doses of 100, 200, and 400 mg/kg, and compared with DXM (10mg/kg), and codeine (5.7mg/kg). *C. albidum* showed significant antitussive activity ($p < 0.001$) in both models (Agbaje and Nzeh 2021).

10.7. *Euphobia hirta and Lactuca virosa*

An investigation was carried out into the di-herbal preparation of *Euphobia hirta* (Euphorbiaceae) and *Lactuca virosa* (Asteraceae) by using whole plant and leaf extract of these plants, respectively. This investigation used two models i.e. citric acid and ammonia-induced cough model in guinea pigs to test the antitussive characteristics of the extract. Combined (100mg/kg E. hirta, 50mg/kg L. virosa), (100mg/kg E. hirta, 100mg/kg L. virosa), only 100mg/kg L.virosa, and 25 mg/kg of codeine lowered the number of cough bouts in the citric acid-induced cough ($P<0.05$), as compared to control. Another combination (50mg/kg E. hirta, 100mg/kg L. virosa), (100mg/kg E. hirta, 100mg/kg L. virosa), and codeine decreased the cough bouts in the ammonia cough ($P<0.001$; $P<0.0001$) when compared with the control group (Uwaya, Bello, and Aikpitanyi 2023).

10.8. Houttuynia cordata

Houttuynia cordata (Saururaceae) is a plant found in the Southeast Asian region, traditionally used for various diseases like diarrhea, and cough. To evaluate the validity of its ethno-medical use as a cough suppressant, a study was conducted by using *H. cordata* plant extract and administering it in guinea pigs with ammonia and citric acid-induced cough. The extraction was made by using various solvents like petroleum ether; benzene; chloroform; acetone; and ethanol, in addition to an aqueous extract. The extract was given at doses of 100, 250, and 400mg/kg. Both the aqueous extract and the ethanolic extract showed significant antitussive activity, particularly at higher doses, in both cough models. This study lent empirical credence to the traditional use of *H. cordata* for antitussive purposes (Warjri and Das 2023).

11. Conclusion and Future Directions

In conclusion, the world is now actively striving to find organic solutions to various problems. This gravitation is informed by globalization and the introduction of more traditional knowledge for treating ailments, in addition to the notorious side effects that come with using Western remedies. As discussed in the article, the mainstream antitussive agents, like codeine and DXM, are not only addicting but also abused widely, leading to grim outcomes and even death in some cases. The plants mentioned in the study not only exhibit potent cough-suppression characteristics but in certain cases, as seen with *Juglans regia*, outperform the standard drugs. Notably, the extracts that performed well in multi-model studies, like *Napoleonaea vogelii*, *Rosa damascene*, and *Hedera helix*, should be seen as attractive options for further research, investment, and drug development for dose standardization. The significant outcomes as well as safety profiles, studied in the investigations, indicate that these drugs can not only substitute but also become cheaper alternatives for those who do not have access to or have addiction tendencies to standard antitussive drugs. A wide-scale replication of these studies, especially in human subjects, and more resource allocation are needed to use these antitussive phyto-extracts to their full potential. The underdeveloped sector of Phytopharmacology is leading to the exploitation of patients and resources.

Conflict of Interest

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All the relevant data of this manuscript is available with the authors.

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