



Review on: Application of Herbal Drugs in the Treatment of Cough

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ABSTRACT

Various herbal sources are used in treatment of common cold or cough like sore throats, coughs, cold, and bronchitis. These cough can be treated by using some common herbal medicine. The literature survey on applications of herbal plants in treatment of common colds is an attempt to collect the information regarding herbal medicines used in the treatment of these cough for benefit of society. Along with herbal treatment the science behind its mode of action in particular disease or disorder is discussed.

Keywords: Application, Cough, Electre, Herbal Medicine, Web

Introduction

Acne vulgarism could be a malady of follicle unit characterized by the formation of open and Closed comedowns, papules, pustules, nodules And cysts. It's the foremost common disorder treated By dermatologists. The term skin disorder comes from Greek word "acme" which suggests "prime of life". Though typically thought-about to be a benign, self limiting condition, skin disorder could cause severe psychological issues or disfiguring scars which will persist for a life.11 acne is that the most common chronic disease of the skin within the United States, touching around eightieth of persons at some purpose between eleven and thirty years of age.1 In one996 within the u. s., the National Health Interview Survey reported the prevalence of skin disorder was 26/1000 in persons <45years of age. Acne vulgarism and rosaceous present therapeutic challenges due to their chronicity, potential for disfigurement, and psychosocial impact. Although path physiological distinct, both conditions have major inflammatory components. Consequently, topical and systemic antimicrobial agents are routinely prescribed for extended periods. 2 Emergence of resistant strains of Propionibacterium acnes, adverse events, and compliance issues associated with chronic systemic tetracycline use have led toned treatment approaches. Doxycycline displays excellent activity against gram-positive and gram-negative aerobic and anaerobic pathogens. 3,4The oral absorption of doxycycline is rapid and virtually complete and is not significantly decreased by food. Moreover, serum concentrations of doxycycline following oral and in intravenous administration are comparable. Because of the prolonged half-life of doxycycline, once daily administration is possible.(1)Doxycycline is highly effective, inexpensive in with a broad therapeutic spectrum and exceptional bioavailability. However these benefits have been overshadowed by its classification alongside the tetracycline's – class D drugs4

Rosacea is a common, chronic dermatologic condition, whose cause remains unknown. It has a higher prevalence in fair-skinned individuals and most commonly affects individuals between the ages of 30 and 50, women being more affected than men.5The diagnosis of rosaceous requires the presence of one or more of the following primary features concentrated on the central area of the face: flushing (transient erythematic), no transient erythematic, papules and pustules, and telangiectasia. Rosacea represents a therapeutic challenge because of its chronic nature, progression, potential for disfigurement, and psychological impact.(6). Doxycycline-treatable diseases area unit rising as leading causes of dedifferentiated symptom unwellness in geographic area. Rosacea is a common, chronic dermatologic condition, whose cause remains unknown.. The medical community often under recognizes the importance of drug induced esophageal lesions and fails to deliver proper advice and instructions related to drug ingestion. The diagnosis is usually clinical although endoscopy is the gold standard diagnostic tool. Treatment is symptomatic with discontinuation of the drug often being sufficient

EXPECTORANT:

What is an expectorant...?

Introduction

Expectorants are ingredients that increase bronchial secretions and make it easier to cough up mucus from the airways and lungs. They are used in the treatment of chesty, wet, productive or phlegm coughs, which typically occur with a cold.

An expectorant is an agent that promotes the secretion or expulsion of mucus from the lungs and air tubes.

Expectorants thin the mucus in the tubes leading to the lungs, making it easier to cough up. Expectorants increase the fluidity of mucus or the rate of its secretion, making the mucus easier to expel. An expectorant is an agent that promotes the secretion or expulsion of mucus from the lungs and air tubes.

An expectorant (from the Latin expectorare, to expel or banish) works by signaling the body to increase the amount or hydration of secretions, resulting in more yet clearer secretions and as a byproduct lubricating the irritated respiratory tract. One expectorant, guaifenesin, is commonly available in many cough syrups. Often the term "expectorant" is incorrectly extended to any cough medicine, since it is a universal component.

Cough:

Cough is a common problem that everyone often faces. Cough is a natural reflex expulsive defense mechanism of the body, for clearing excess secretions or mucous or inhaled irritants or toxins or foreign substance in the respiratory tract. Coughing protects the respiratory system by clearing or cleaning it voluntarily or involuntarily. As long as cough is helpful in getting rid of infectious material with the help of mucous from the airway, it should not be stopped. It is very important to remember that cough usually manifests in common cold, but it may be the initial manifestation of serious illness such as pulmonary hypertension, pneumonia, tuberculosis or asthma. It can be in various situations inappropriately stimulated; for example, by inflammation in the respiratory tract or neoplasia. (Schroeder, K. et al., 2002) In these cases, the cough has a pathological character and it is necessary to use cough-suppressing agents. Anti-tussive agents are used mainly to suppress dry and painful coughs [1].

Mechanism of Cough:

Cough serves to clear the airways when there are large amounts of inhaled material, mucus due to excessive secretions or impaired mucociliary clearance and abnormal substances such as edema fluid or pus. Each cough involves a complex reflex arc. The cough reflex has five components: cough receptors, an afferent nerve (the vagus nerve), the cough center (area in medulla), motor (efferent) nerves (recurrent laryngeal nerve, phrenic nerve and spinal nerves) and effector organs (the diaphragm, chest and abdominal wall muscles) (Chung, K.F. (2003). Cough receptors are located along the entire laryngo-tracheo-bronchial tree with the greatest number in the larynx. They are also located in the nose, paranasal sinuses, diaphragm, pleura, stomach and pericardium. There are three types of nerve fibres, which form the sensory (afferent) pathway leading to cough

Myelinated irritant fibres

Unmyelinated C fibers

Slow adapting stretch receptors

Nerve endings in the larynx, trachea and bronchi are sensitive to irritation that generates nerve impulses which are conducted by the vagus nerves to the respiratory center in the brain stem. The reflex motor response is deep inspiration followed by closure of the glottis (Sesuka S, et al 1985) the internal laryngeal nerve, a branch of the superior laryngeal nerve, carries the sensory information away from the area above the glottis in the larynx to the CNS via cranial nerve X (vagus). The receptors report about the excess mucous or foreign substance to the cough center which is located in the medulla of the brain for inducing cough. The abdominal and respiratory muscles then contract and suddenly the air is released under pressure expelling mucus and/or foreign material from the mouth. Cough receptors are sensitive to:

Touch of inhaled foreign body like plant

Excessive secretions or mucous in nose, throat, sinusesAnd lungs

Irritant gases like nitric acid, sulphuric acid, ammoniaAnd sulphur dioxide

Oedema or infection with pus in the airway

Exposure to extreme hot or cold air

The mechanism of a cough is as follows:

Coughing is started by stimulation of sensory nerves in the lining of the respiratory passages - the tubes used to breathe.

Diaphragm and external inter-costal muscles contracts, increase the volume of the lungs and makes the pressure of air within the lungs lower than atmospheric pressure.

Air rushes into the lungs in order to equalize the pressure.

The glottis closes (muscles innervated by recurrent laryngeal nerve) to prevent air escaping whilst the diaphragm relaxes and expiratory muscles contract.

This reduces the volume of the lungs, therefore increasing pressure.

The pressure of air within the lungs is now greater than atmospheric pressure and so air is trying to escape. Thus, glottis opens and release air at over 100 mph [1].

Phases of Cough Coughing involves four phases. These are as follows:

1) **Inspiration:** -The initial phase of cough is characterized by the inhalation of gas. During inspiration, the expiratory muscles are lengthened and strengthened. Thus, inhaling to high lung volumes will enable the expiratory muscles to generate greater positive intra-thoracic pressures for a given degree of neural activation. Although a modest degree of positive intrathoracic pressure is needed to generate expiratory flow, an effective cough can be

achieved at pressures much lower than the maximal pressure that the expiratory muscles are capable of producing. Thus, this initial phase of cough is not critical because an effective cough can be accomplished by inhaling small volumes (Mazzone, S.B et al 2002).

2) **Compression** of air against a closed glottis:-The compressive phase of cough follows the initial inspiratory phase. After inhaling a volume of air, the glottis is closed and an expiratory effort ensues. At the onset of the expiratory effort, the glottis closes for about 0.2 seconds. Glottis closure maintains lung volume as intra-thoracic pressures are building. Glottis closure minimizes expiratory muscle shortening, thereby promoting contraction of the expiratory muscles, and allowing the expiratory muscles to maintain a more advantageous force-length relationship and to generate greater positive intra-abdominal and intra-thoracic pressures. The high intra-thoracic pressures developed during glottis closure may be as great as 300 mm Hg. The closed glottis also creates a pressure drop (high pressure inside, low pressure outside) so that when the glottis opens, the air is forcefully expelled to outside (Dicpinigaitis, P.V. 2003)

3) **Expression**:-Once the glottis is opened, the expiratory phase of cough ensues, and the high intra-thoracic pressures developed during the compressive phase of cough promote high expiratory flow rates. The glottis is opened and the airways collapse to expel the cough (and whatever it may carry). Initially, there is a very brief blast of turbulent flow. This burst of air is due to the additive effects of the gas expired from the distal parenchymal units and the gas displaced by the central airways, which are compressed by the high intra-thoracic pressures. Although glottis closure enhances this phase of cough, it is not essential for an effective cough. For example, individuals with a tracheostomy or endotracheal tube can produce an effective cough by performing a huffing maneuver, which is performed with an open glottis.

4) **Relaxation**:-After the cough reflex the expiratory muscles relaxed and there is a transient bronchodilation (McCool, 2006).

Causes of Cough:

1) **Infection**:by bacteria, virus (common cold), and fungus (Aspergillus infection).

2) **External factors**:-by dust, cold, pollens, smoking and other environmental irritants. Also the drugs, which used in treatment of hypertension and heart diseases (ACE inhibitors and beta-blockers) may cause cough. Foreign body when enters pharynx, nose, larynx, trachea, bronchus, oesophagus. (Widdicombe, J.G. 2002)

3) **Internal factors**:as diseases get progressive in: (Sinuses - Postnasal drip (Heart - Congestive heart failure (Lung - Asthma, chronic bronchitis, cancer, pneumonia, tuberculosis and pressure on lungs due to a mass like mediastinal lymphadenopathy. (Ear - Otitis media, and foreign body (Stomach – Gastro-oesophageal reflux

4) **Psychogenic factors**: habit of clearing mucous, for drawing attention, etc. (Lee, L.Y.et al. 2001).

Symptoms of Cough:

Cough itself is a symptom, usually associated with sore throat, hoarseness, nose block, breathlessness, heartburn or chest pain, dizziness, disturbance in sleep, distress on exercise or running, sometimes even for laughing, restlessness, general bodyaches, urinary incontinence, haemoptysis, lack of concentration, stomachache, nausea, vomiting and swollen glands. It produces white/green/yellow/ discolored or blood-stained phlegm (Eccles R et al.1992). The high intra-abdominal and intra-thoracic pressures developed during compressive phase of cough can be transmitted to the CNS and mediastinum, and underlie some of the adverse cardiovascular, GI, genitourinary, musculoskeletal, and neurologic complications associated with cough. Some effects of cough on the body organs during coughing are as follows:

Pressure in abdomen is increased - so hernia may occur in diaphragm or the muscle of the abdomen (umbilical hernia, incision hernia) or into the scrotal sac.

The anus will get tightly closed - so it may aggravate piles or fissure in the anus.

Due to pressure in chest - air emphysema may develop.

Due to violent cough, bursting type of headache may occur. (Feldman JI et al. 1993.)

Types of Cough

Cough mainly classified as:

1) **Productive Cough** it is also termed as an effective cough and wet cough, since it effectively expels secretions, mucous or foreign material from the respiratory tract. This type of cough is mostly acute in nature and often caused by bacterial or viral or fungal infection. This type of cough should not be suppressed or otherwise recurrent or constant infection will be there, since the purpose of the cough (to remove mucus) is suppressed. Productive cough should be allowed to serve its purpose and suppressed only when it is exhausting the patient or is dangerous, e.g. after eye surgery (Karlsson, J.A.1996).

2) **Non-productive Cough** It is also named as an ineffective cough since it won't bring any secretions or mucous from the lungs. It is a dry, irritating cough without phlegm. Mostly, this type of cough is chronic in nature and caused by dry irritation or dust or smoke or fumes, or due to edema and mild secretion in the resolving stage of illness. Dry cough is mainly useless and persistent in nature, thus it should be stopped. Asthma, rhinosinusitis,

esophageal reflux or combination of the last two is the commonest underlying reason for persistent cough. It may be also due to weakness of the muscles of respiration, thick viscid mucus and in diseases of the cilia which helps mucous transportation in the airway. The overall approach to the persistent cough must involve attention to underlying factors (Bennett and Brown, 2003).

Cough can also be classified as:

Acute - not more than three weeks' duration - for example, infective coughs

Chronic - more than three weeks' duration - for example, smoker's cough

Dry cough - no mucous or secretions

Wet cough - with mucous or secretions

Cough from chest and cough from throat - productive or non-productive

Paroxysmal cough - spasmodic and recurrent (Bovine cough - soundless cough due to paralysis of larynx)

Psychogenic cough - self-conscious activity of the patient to draw attention

EXAMPLES OF HERBAL COUGH PREPARATION:

Formulation:

1) Joshina (Hamdard)

Ingredients

Glycyrrhizaglabra, Viola odorata, Althaea

Officinalis, Cordia latifolia, Onosmabraceatum,

2) Baidyanath -Kasamrita Herbal Syrup

Ingredients

Somlata, Kantakari, Vasakmool, Mulethi,

TulsiPanchang, Lisora, Gazoban,

Kakadsingi, Pipa.Nausada, PudinaSatva [17].

3) Zeal Cough Syrup (Medi Power Co.,Ltd)

Ingredients

Extract derived from Ocimum sanctum,

Adhatodazeylanica, Glycyrrhizaglabra, Navsagar,

Zingiberofficinale, Solanum Xanthocarpum,

Trikatu, Sat, Peppermint 6mg, NilgiriOil [17].

4) Koflet Cough Syrup (Himalaya)

Ingredients

Vitisvinifera, Ocimum sanctum,

Glycyrrhizaglabra, Adhatodavasica,

Viola odorata, Onosmabraceatum,

Solanum xanthocarpum, Embeliaribes, Cinnamomum cassia.

5) Kafbin (East India Pharmaceuticals)

Ingredients

Glycyrrhizaglabra, Piper longum, Piper nigrum,

Zingiber officinalis, Solanum xanthocarpum,

Terminiliabellerica, Clerodendrumindicum [17].

6) Dabur Honitus Herbal Syrup

Ingredients

Ocimum Sanctum, GlycyrrhizaGlabra,
 Solanum Xanthocarpum, Viola Odorata,
 TaxusBaccata, ZingiberOfficinal, Piper Longum,
 AdhatodaVasica, Hedchium Spicatum, Menthe PiperitaExtract [17]

7) D'cold Natural (Paras Pharmaceuticals Ltd.)

Ingredients

Ocimum sanctum, Glycyrrhizaglabra, Adhatodavasica,
 Curcuma longa, Alpinialgalasya, Piper longum, Zingiber officinalis,
 Menthaviridis, Honey [17].

❖ **Herbal Expectorant Formulation:**• **Procedure/Preparation of kadha :**

- Add all powder ingredient (Ashwagandha, Tulsi, Yashtimadhu, Ginger, BlackPapper, Cardamom) in sufficient ml of lukewarm water stepwise and shake with spoon. (Lukewarm water is better effect)
- Add 2 cups of water are boil & reduce half volume, cool the preparation.
- Add about 1or ½(quantity sufficient) spoonhoney and shake it. (Diabetic patient are not use honey)
- Add few drop of lemon (according to the taste)
- Sip it slowly
- After taken the formulation don't drink extra water and eat at least for 10 min.

Dose:

- 5gm of powder in 1 cup of lukewarm water

Direction:

- At night after meal when you sleep that time give for minor cough or cold.
- In serious condition, take two timesafter meals at night and early morning.

Yashti-madhu (Glycyrrhizaglabra) :

It is the dried roots and rhizomes of Glycyrrhizaglabra and is commonly knownasMulathee3. It is an erect, perennial plant grown in sub-tropical and warmtemperate regions of Mediterranean countries and China. The major chemicalconstituents of this plant include triterpene saponins like Glycyrrhizin whichoccurs as a mixture of potassium and calcium salts3 and renders the plant its sweet taste. Traditional application involves its use against sore throats and asanexpectorant in treating coughs and bronchial catarrh. It is also a laxative and antiviral drug with remedial properties of kidney stones, heart disease,loss of appetite and snake bite3. It also possesses antioxidant and antipyreticproperties13. The aqueous and ethanolic extracts of this plant have shownnitric oxide-, superoxide- and hydroxyl - radical scavenging activities. The hydro alcoholic extract of this plant also demonstrated antioxidant property through modulation of respiratory burst of human activated neutrophils [5].

Tulsi (Ocimum sanctum):

Tulsi is the common name for "Sacred Basil" or "Holy Basil" and belongs to thefamilyLamiaceae. It is an erect, herbaceous, branched, biennial or triennial plant,30 – 75 cm high14. In India, two types of this species can be seen – the green Sri Tulsi and the purple Krishna Tulsi14. The plant is worshipped by Hindus and is a common plant grown in almost all Indian houses. Its use dates back to 5000 BC, wherein traditional benefits from this plant find mention in Charak

Samhita and Rigveda. The leaves of this plant contain a bright yellow volatile oil composed of sesquiterpenes (the main one is Eugenol) and monoterpenes. This oil has shown antibacterial and insecticidal properties. Essential oil obtained from this aromatic plant is used as fragrances and, flavors in food industries15.

It has antifertility, hepatoprotective, antidiabetic, anticancer, and cardioprotective

properties¹⁶. Household remedy involves taking eleven Tulsi leaves with four black pepper seeds to treat Malaria and Periodic fever; juice of leaves mixed with honey and ginger for treating bronchitis, asthma, influenza, cough and cold, by mobilizing mucus¹⁵. It is also effective in curing ringworm and other skin diseases. Pills prepared from crushed mixture of fresh Tulsi leaves, *Leucasaspera* leaves, *Momordicacharantia* leaves and dried fruits of *Piper longum* are advised twice a day for one week for treating asthma⁶. Since, Tulsi is immunomodulatory, antitussive and expectorant in action, it finds wide applications in pharma companies for manufacturing newer drugs and formulations containing this plant against cough, acute and chronic bronchitis, asthma and other respiratory ailments. Immunomodulatory action is carried out by this plant through an increase in Interferon- γ , IL-4, T-helper cells, NK cells, thereby reducing bacterial load through phagocytosis¹⁷. In vivo studies on histamine and acetylcholine-induced pre-convulsive dyspnea in guinea pigs have shown the anti-asthmatic activity of 50% aqueous-ethanolic extract of Tulsi¹¹. It has been reported to be a strong antioxidant against oxidative stress, genotoxicity and imbalanced xenobiotic-metabolizing enzymes induced by 7, 12-dimethylbenz [a] anthracene in rats [6].

Ginger (Zingiberofficinale):

Ginger is a tropical plant grown in India, Malaysia, Southern China and Japan, and India is the world's largest producer³. It belongs to the family Zingiberaceae, known commonly as adrak, and possesses characteristic aroma and taste. It is a powerful natural expectorant used in treating cold, cough and chronic bronchitis. It contains 1-4% essential oil, sesquiterpene hydrocarbons, and gingerols (responsible for the pungency of ginger)[8]. It possesses anti-inflammatory, anti-viral, anti-nausea and antiemetic activities. Ginger acts as a carminative, gastrointestinal stimulant and antidepressant⁸. Traditional application involves intake of 20 ml of ginger juice mixed with betel leaves and honey three times a day for three days to treat cough and cold⁶. In vivo studies have shown ginger as hypolipidemic (ethanolic extract of ginger lowered cholesterol level in rabbits), chemoprotective (aqueous or ethanolic ginger extract showed antitumour properties in mice), and anti-inflammatory (oral administration of ginger oil to arthritis induced rats showed significant suppression of inflammation) agent⁷. It also showed antioxidant potential in acetaminophen-induced oxidatively stressed rats [7].

Ashwagandha (Withaniasomnifera) Ashwagandha (Latin):

Withaniasomnifera, also known as winter cherry Or Indian ginseng is both a tonic and a sedative due to its adaptogen Properties [9]. *Withania* refers to the plants primary extract and *somnifera* literally means "sleep-inducing" [10]. The name *ashwagandha* is derived because of two reasons – the roots of the herb smell like a horse and, there is a commonly held belief that a person consuming extracts of the herb may develop the strength and vitality similar to that of a horse. *Ashwagandha* is also known as the "SattvicKaphaRasayana". "Rasayana" is Sanskrit and literally means "path" (ayana) of the "rasa" (fluid or juice). According to Sushruta, rasayanas are the substances that slow the ageing process, increase longevity and increase strength, both mental and physical⁶. Used in India for thousands of years as a common home remedy, *ashwagandha* is one of the most versatile medicinal plants in Ayurvedic Medicine with a wide spectrum of actions and applications. *Ashwagandha* is most commonly administered as a "churna", a fine sieved powder that can be mixed with ghee, honey, milk or water. *Ashwagandha* is one of the most Used in expectorant in treating coughs, Influenza, Bronchitis, Asthma, Epilepsy, Depression, Allergies, Goiter. Though all parts of the plant are used, it is the root that provides the most pharmacological effect as the major extract - withanoloids (combination of steroidal alkaloids and lactones) are contained therein [9].

Cardamom:

Cardamom is the dried fruit of the tall perennial herbaceous plant, *ElettariacardamomumMaton*, and belonging to the family Zingiberaceae (3). This herb is cultivated commercially in India, Sri Lanka, Guatemala and Tanzania. The leaves are lanceolate, green or dark green, glabrous on both surfaces with acuminate apex. The fruit are tri-ocular, ovoid, oblong or greenish-brown capsules containing about 15-20 reddish brown seeds. The cardamom seeds have a warm, slightly pungent and highly aromatic flavour. The chemical composition of cardamom varies considerably with Variety, region and age of the product. The content of volatile oil in the seeds is strongly dependant on storage conditions. The basic cardamom Aroma produced by a combination of the major components, 1,8-cineole and α - terpinyl acetate (12). Cardamom oil is used in food, perfumery, and liquor a pharmaceutical industries as a flavour and a carminative. In medicine, it is used as a powerful aromatic, antiseptic, stimulant, carminative, stomachic, expectorant, anti-spasmodic and diuretic (5, 11).

Honey:

The World Health Organization regards honey as a potentially valuable demulcent for the treatment of cough [11]. Honey is a sweet viscous liquid with a complex chemical composition of carbohydrates, free amino acids, vitamins, trace elements and flavonoids. It also contains compounds that function as antioxidants. It is said to possess anti-bacterial, antiviral and anti-inflammatory properties. [14]

Studies of the antimicrobial effect of honey have demonstrated its broad-spectrum antimicrobial actions against various gram-positive and gram-negative bacteria. It is also active against common bacteria found in the upper respiratory tract such as *Staphylococcus aureus* and *Streptococcus faecalis*, amongst others.¹⁴ Honey has been used in traditional medicine for the treatment of cough and is used in modern medicine to treat wounds and aid healing processes. The use of honey is prohibited under the age of one due to poor immunity against *Clostridium Botulinum*, a potential contaminant.

A review by Eccles, argues that the sweetness of liquid preparations used to treat cough accounts for much of the observed effect. The hypothesis suggests sweet substances naturally cause reflex salivation and production of airway mucus leading to a demulcent effect on the pharynx and larynx, thereby

reducing cough. It is suggested that there is interaction between opioid-responsive sensory fibers and the gustatory nerves to help produce an antitussive effect via the central nervous system.

Honey has been shown to be a better treatment for coughs than dextromethorphan. Keep in mind that there are a number of reasons why you cough and that coughing does serve a purpose. But sometimes the coughing can get excessive and honey is a proven natural cough suppressant.

Honey is also good at loosening up that congestion in your chest. Which will make your coughs more effective. This makes it a natural expectorant. There are other expectorants that you can take such as various teas. I would suggest mixing in a little honey with these to get a more potent affect. It is important to note that you should never give honey to babies. Wait until they are over 1 year old first [11].

Conclusion

From the results of trials to determine herbal cough medicines with trials of several Plants from 4 categories of coughing the system can provide recommendations for Medicinal plants according to the cough symptoms that have been chosen. The test results Of the alpha tests that have been carried out indicate that the application built has met the Functional requirements. And beta testing that has been done, namely by testing the Calculation of the choice of answer categories from the questionnaire that has been Distributed can be concluded that the software built is easy to use and has a pretty good Appearance. So that the application of the selection of herbal cough medicines makes it Easier for people to choose and recognize medicinal plants that are suitable for coughing Suffered and how to circumvent herbal medicines.

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