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FORMULATION AND EVALUATION OF HERBAL COUGH SYRUP

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ABSTARCT

Zingiber officinale is a locally available plant in India that is extensively utilized as a flavoring agent in sweets like cakes and biscuits, savory foods like curries, and alcoholic beverages. as in tea. A well-known herb, ginger is frequently utilized in traditional medicine across the globe. Ginger has been used for thousands of years to treat high blood pressure, arthritic pain, colds, nausea, and headaches. Antiemetic, antidiabetic, analgesic, anti-arthritis, antioxidant, anti-cancer, anti-ulcer, antibacterial, anti-inflammatory, estrogenic, and cardiovascular are only a few of the numerous pharmacological properties of ginger. Ginger's strong flavor is caused by an unsaturated liquid phenolic ketone (C₁₇H₂₄O₃) and a chemical stimulant. Ginger's primary constituents are pungent oleoresin, antioxidants, and fragrant essential oils. For the first time, the current study demonstrates that raising the drying and extracting temperatures of ginger can enhance the production of 6-shogaol during the practical drying and extraction process. Increasing the pH of the extraction solvent with strong acid also aids in producing more 6-shogaol. Our information may be helpful to the food processing and nutraceutical industries. Functional foods can provide health benefits because they contain compounds that are physiologically good for health. The level of public awareness about healthy living through food and drink needs to be increased. This awareness can be obtained through the composition of food and drink that has an attractive taste and color without neglecting certain physiological functions contained in the food or drink so that it is beneficial for the human body. One of the drinks that contain food additives in the form of synthetic dyes is syrup. Many syrups marketed are made of synthetic flavours, artificial sweeteners and synthetic dyes which of course if consumed in the long term can interfere with the health of human organs, so there needs to be innovations in making herbal syrups such as the use of emprit ginger and lime rhizomes.

KEYWORDS – Gingerol, Cough Syrup , Zingiber officinale , Expectorant, Antioxidant.

INTRODUCTION[23,24,25]

Ginger (Zingiber officinale Roscoe) is a herb that has been used for thousands of years to treat a variety of ailments, including gastrointestinal, stomachic, rheumatic, and muscular discomfort. The herb's origins can be traced back to Southeast Asia and its widespread spread to the rest of the world. Ginger has been shown to have anti-inflammatory and antioxidant properties in a number of recent research. Furthermore, gingerol, paradol, shogaol, and zingerone—non-volatile pungent derivatives of oleoresin from ginger—are said to have chemotherapeutic properties . Gingerols, or homologous phenolic ketones, are typical bioactive chemicals found in ginger. They are classified as 6, 8, and 10-gingerols, depending on the length of their unbranched alkyl chains . Ginger (Zingiber officinale Roscoe, Zingiberaceae) is one of the most commonly

consumed dietary condiments in the world. The oleoresin (i.e., oily resin) from the rhizomes (i.e., roots) of ginger contains many bioactive components, such as [6]-gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone; which is the primary pungent ingredient that is believed to exert a variety of remarkable pharmacological and physiological activities. Even after the fall of the Roman Empire, ginger remained a highly sought-after item in Europe, controlled by Arab traders.

commerce of spices, including ginger, spanning centuries. A sheep could be purchased for the equivalent of one pound of ginger in the 13th and 14th centuries. During the Middle Ages, raw and preserved ginger was brought to Europe and was a staple of many nations' official pantries. It was imported as canned goods to be used as confections during the Middle Ages. The classic Christmas dessert known as anthropomorphic gingerbread is linked to Queen Elizabeth I of England. Gingerols show significant anti-cancer properties against skin cancer in vivo and stomach and colon cancer in vitro. It has been discovered that 6-gingerol, one of the gingerols, has a variety of pharmacological properties, such as anti-inflammatory, analgesic, antipyretic, chemopreventive, angiogenesis, and antioxidant application.

HERBAL SYRUP^[1,2]

Herb syrup is prepared by adding a concentrated herbal extract with sugar, and alcohol was also used. Herbal syrup was made with decoction. Mixing a decoction of herbs with sugar helps to thicken the recipe and preserve it. This increases the shelf life of the formula. Added sweeteners can also help enhance the taste of certain herbs. The resulting syrup is delicious! It is defined as a thick, sticky liquid consisting of a concentrated solution of sugar and water with or without added flavoring or medicinal ingredients.

• ADVANTAGES OF SYRUP

- 1) Nausea relief.
- 2) Encouraging stomach emptying can relieve the discomforts of nausea.
- 3) Bloating and gas.
- 4) Eating ginger can cut down on fermentation, constipation and other causes of bloating and intestinal gas.
- 5) Ginger is used in anti-inflammatory.

Aim :- Formulation and evaluation of herbal cough syrup.

Objectives

- 1) Most of herbal syrup was originally derived from plant herbal medicine refers to use extract of fruit for medicinal purpose.
- 2) Along with other dosage from herbal drugs also formulated inform of syrups.
- 3) Today syrup is used for treatment of many ailments and to overcome symptoms of diseases.
- 4) It can relieve symptoms of cold and cough such as congestion coughing and sore throat.
- 5) It can help soothe and improve the respiratory system.

Following are the ingredients used in formulation.

- 1. Ginger:** It is used in various herbal and ayurvedic treatment of cancer. The Soxhlet extracted alcoholic extract was obtained which was further filtered and used.
- 2. Orange oil:** It consist fruit of plant citrus aurantium belonging to family: Rutaceae. It contain not less than 2.5% of volatile oil. It uses as antioxidant, anti-cancer and neurodegenerative disorder.
- 3. Alcohol:** It uses in small quantity act as preservative.
- 4. Invert sugar base:** It was prepared by mixing 2 cups (480 mL) of water with 4.4 cups (1 kg) of granulated sugar and 1/4 teaspoon of cream of tartar in a pot.

BIOACTIVE COMPONENTS OF GINGER^[3,4,5]

At least 115 constituents in fresh and dried ginger varieties have been identified by a variety of analytical processes. Gingerols are the major constituents of fresh ginger and are found slightly reduced in dry ginger, whereas the concentrations of shogaols, which are the major gingerol dehydration products, are more abundant (Jolad et al. 2005) in dry ginger than in fresh ginger. At least 31 gingerol-related compounds have been identified from the methanolic crude extracts of fresh ginger rhizome (Jiang, Solyom et al. 2005). Ginger has been fractionated into at least 14 bioactive compounds, including [4]-gingerol, [6]-gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-

gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4' hydroxyl-3' methoxyphenyl)-5-methoxyheptan-3-one, and methoxy-[10]-gingerol (Koh et al. 2009)

Herbal syrup was made using the decoction technique. Herbal Creations Pvt Ltd provided the fine extract used to make the ginger extract. The extract by which an ethanolic extract was made.

HISTORY:^[6,7,8]

In 1895, German drug manufacturer Bayer released its latest cough syrup, which they sold under the brand name "Heroin". Traditional cough syrup mixtures are formulated around in syrup at 60-75 % concentration which is made from sucrose, maltodextrin, glucose, invert syrup. The cough syrup was manufactured by Fourrts Laboratories in india.

DIAGNOSIS OF COUGH

These frequently include methacholine challenge testing, sputum (mucus) testing, imaging studies including CT scans or X-rays of the chest, spirometry, and blood tests. It could be a good idea to have the following information ready in advance to aid your doctor in making an accurate diagnosis. Acute bronchitis and acute viral upper respiratory infections, commonly referred to as the common cold, are the most frequent causes of acute cough in adults. The aetiology of acute bronchitis is mostly viral, however in around 10% of cases, bacterial infection is the cause. January 2024.

TYPES OF COUGH ^[9,10,11]

Classifying coughs as wet or dry is the easiest method to understand them. Mucus-filled coughs, or wet coughs, are frequently happen when one has the flu, a cold, pneumonia, or another sickness. The process of clearing the respiratory system of mucus causes the patient to feel sticky and moist in the back of their throat. When a cough doesn't generate mucus, the throat feels dry and tickly. They often arise from inflammation of the digestive tract brought on by asthma, croup, allergies, and other diseases. Depending on the type of cough, you can select a dry cough syrup or a suitable wet cough syrup designed to address the particular issue.

CHRONIC COUGH TREATMENT^[12,13]

Upon reviewing the secondary sources excluded from the Cochrane Collaboration, we found one that did not meet the minimal systematic criteria, which we opted not to include^[9,10,11] Rather, the CDSR offers a "umbrella review," which is made up of up to 15 SRs and is updated on a regular basis on the internet, offers a substantial, comprehensive, and ethically sound body of evidence. However, due to the overall dearth of well-structured trials on pharmaceutical and non-pharmacological therapy for childhood persistent cough, it currently lacks broad therapeutic value. Among these fifteen SRs, one looked at the management algorithms that were previously discussed in this study.

PHRMACOLOGICAL ACTION ^[14]

Decongestants The decongestants found in children's OTC cold medication are either pseudoephedrine or phenylephrine. Systemic decongestants are adrenergic receptor agonists (sympathomimetics) that produce vasoconstriction within the mucosa of the respiratory tract, temporarily reducing the swelling associated with inflammation of the mucous membranes.^[12,13] Sympathomimetic drugs work on the α receptors in the vascular smooth muscle causing vasoconstriction and presser effects and on the β adrenergic receptors in the heart causing increased heart rate and force of contraction.^[14,15] Because of the cardiac effects, these agents should be used with caution in children with congenital heart disease, hypertension, or cardiac arrhythmias without consulting the patient's pediatric cardiologist.. Oral decongestants also should be used with caution in patients with hyperthyroidism and diabetes mellitus. Topical decongestant products are applied topically to the nasal tissues via spray or drops. Topical decongestants stimulate the α -adrenergic receptors in the arterioles of the nasal mucosa, leading to vasoconstriction and shrinkage of nasal tissues. There is minimal systemic absorption if used as directed. The use of isotonic saline nose drops and gentle aspiration can be effective in the temporary relief of nasal obstruction in infants. Also useful is the general humidification of room air. Moisture tends to dilute tenacious nasal mucus so that it is easier to remove.

Cough Suppressants Dextromethorphan is the cough suppressant found in OTC cough medications, and it often is combined with the expectorant guaifenesin. Dextromethorphan, the D isomer of the codeine analogue levorphanol, acts centrally in the cough center in the medulla to suppress cough. Drowsiness, dizziness, nausea, and gastrointestinal upset also may be seen with dextromethorphan use. Diphenhydramine, an antihistamine, also is marketed as a cough suppressant for The exact mechanism of action of first generation antihistamines antitussive effects is unknown. Expectorants Guaifenesin is the most

commonly prescribed oral mucolytic agent as an expectorant in the United States. Its mechanism of action is to reduce the surface tension and viscosity of the mucus, which increases the ease of expectoration. Respiratory mucus removal is facilitated by increased flow of the thinned secretions via ciliary action.[36] Studies on the efficacy of guaifenesin have failed to demonstrate either improved pulmonary function or decreased sputum viscosity. Hence, its clinical usefulness is questionable. Antihistamines Diphenhydramine, chlorpheniramine, and brompheniramine are the antihistamines found in children's cold and allergy formulas. Antihistamines, also known as H1 receptor antagonists, compete for and block the action of histamine at the H1 receptor site on cells in the respiratory tract, gastrointestinal tract, and blood vessels. In the respiratory tract, antihistamines decrease congestion related to allergies.[40] Naclerio et al 1988 studied the response of inflammatory mediators to induced viral infections. All variables except histamine grew stronger in direct relationship with the symptoms as the cold increased in severity. This finding indicates that antihistamines have no role in the treatment of the common cold; they will not shorten the period of symptoms. They are helpful, however, treatment of the symptoms of allergic rhinitis. Lastly, in young infants, sympathomimetic-antihistamine mixtures are particularly dangerous because they may cause respiratory depression. Antipyretics Some multi-symptom cold formulas contain acetaminophen or ibuprofen as an antipyretic and analgesic. Acetaminophen acts centrally to inhibit the synthesis of prostaglandins in the CNS and peripherally to block pain impulse generation. Antipyretic activity is due to its action against prostaglandin E2 in the CNS, which increases in fever.

ACTIVE INGREDIENTS FOUND IN HERBAL REMEDIES THAT POSSESS AN ANTITUSSIVE EFFECT^[15,16]

Saponins

Among herbal remedies, saponins are one of the most well-understood mechanisms of action, with the capacity to modify cough characteristics and phlegm quality. Heterosides with both glycid and non-glycid components are called saponins. The non-glycid component, referred to as the aglycone, is responsible for its pharmacological effects. When therapeutic doses are taken orally, the saponins reflexively irritate the vagal nerves. This leads to an increase in phlegm output in the airways. Moreover, expectoration is elevated due to inflammation in the cough and respiratory centres. Conversely, larger concentrations of saponins can irritate the stomach and intestinal mucous membranes, leading to emesis, diarrhoea, and bleeding.

Flavonoids

Flavonol glycosides and their aglycones combine to form flavonoids. Activation can be decreased by flavonoids of xanthinoxidase and cholinesterase by preventing oxidative and reductive processes. The antitussive-expectorant activity of flavonoids, which are used to treat renal diseases, thromboembolic sequelae, and cardiovascular illnesses, is probably what makes their therapeutic benefits advantageous.

Essences

Essences are compounds that include fragrant terpenes. These are volatile substances that directly stimulate cells that secrete, irritating a range of bodily tissues, including the epithelium of the airways. They accelerate the ciliary epithelium's motility and have antibacterial and antiphlogistic qualities. The ingredients in the essence medications are Fructus anisi, Fructus foeniculi, Fructus melissae, H. seu, and Fructus thymi. and renal parenchyma damage are some of the side effects that might occur after using aetheric oils.

Mucilage

These days, upper respiratory infections are frequently treated with the so-called slime medications. connected to a dry, uncomfortable cough. The most well-known are Folium et Flos althaeae, Folium et Flos malvae, Radix, and Folium plantaginis. Slime medications create a protective layer on the surface of the airway mucous membrane that lessens irritation of the nerve endings of nonmyelinated C-fibers as well as cough receptors (rapidly adapting cough receptors, or RARs) on myelinated vagal nerve fibres. This lessens the irritation of the injured mucous membrane brought on by inflammatory mediators or foreign objects, which results in coughing

Gums

Gums are transparent, amorphous hydrocolloids found naturally in plants, usually found in higher plants. as a post-injury protection agent. The herbal gums have a strong antitussive effect. The antitussive qualities of peach gum were studied. Mucilage's cough-suppressing properties are probably comparable.

Pectin

Pectin is said to as a mucous membrane protector for the stomach. The exact mode of action of pectins is unknown, but in experimental settings, the antitussive effect of pectins isolated from citrus fruits (30.2 percent) was comparable to that of antitussives that act peripherally, like prenoxidiazine (23.7 percent) and dropropizine (27.4 percent) (dose of 50 mg/kg b.w.).

MATERIALS AND METHODS.^[17,18]

To use the Soxhlet extraction method to extract the active ingredients that are unique to ethanol. The extract was then further filtered, and aliquots of the amounts specified in the table were utilized to create formulations F1 through F4. After combining all of the extracts, 50 milliliters of syrup were produced. The hue flavoring agent and agent are added to it. The resulting syrup was poured into an amber bottle, sealed, and kept in a cool, dry location.

Table 2: Formulation No.1 (F1) - For 100ml

| Sr. No | Ingredient | Quantity |
|--------|-------------------|----------|
| 1) | Ginger extract | 14ml |
| 2) | Orange oil | 10ml |
| 3) | Invert Sugar Base | 76ml |

Table 3: Formulation No.2 (F2) - For 100ml

| Sr. No | Ingredient | Quantity |
|--------|-------------------|----------|
| 1) | Ginger extract | 10ml |
| 2) | Orange oil | 4ml |
| 3) | Invert Sugar Base | 66ml |
| 4) | Alcohol | 20ml |

In above formula (F2), we used alcohol because in the formulation number 1 (F1), sugar was not able to inhibit the growth of fungi, so we use alcohol.

Table 4: Formulation No.3 (F3) - For 100ml

| Sr. No | Ingredient | Quantity |
|--------|-------------------|----------|
| 1) | Ginger extract | 16ml |
| 2) | Orange oil | 4ml |
| 3) | Invert Sugar Base | 66ml |
| 4) | Alcohol | 14ml |

The formulation number 2 was rejected because of more quantity of alcohol is use. In this formula we use alcohol as minimum quantity.

Table 5 : Formulation No.4 (F4) - For 100ml

| Sr. No | Ingredient | Quantity |
|--------|-------------------|----------|
| 1) | Ginger extract | 30ml |
| 2) | Orange oil | 8ml |
| 3) | Invert Sugar Base | 40ml |
| 4) | Alcohol | 22ml |

EVALUATION PARAMETER^[19,20,21]**1)Density**

Density It was evaluated by Formula as given below, Formula for density: Density of liquid under test (syrup) = weight of liquid under test /volume of liquid under test = w_3/v .

2)Specific gravity Specific Gravity was evaluated by the formula as given below Specific gravity of liquid under test (syrup) = weight of liquid under test /weight of water = w_5/w_4 .

3)Viscosity

Viscosity 2.2.1. Viscosity was determined using the following formula Density of test liquid × Time required to flow test liquid Density of water × Time required to flow water.

4)PH pH was determined on pH meter.

COLLECTION OF PLANT MATERIAL

The rhizome of *Zingiber officinale*, Orange peel were collected from adjoining area of Shrigonda (Ahemedngar) in the month of June- 2023.

HERBS USED IN COUGH SYRUP

DRUG PROFILE

1.GINGER



Fig no.1.GINGER

Biological Source : Ginger is a flowering plant whose rhizome of *Zingiber officinale* .

Family : Zingiberaceae

Chemical constituents : Ginger is abundant in active constituents, such as phenolic and terpene compounds and paradols. In fresh ginger, gingerols are the major polyphenols.

Uses :

- Expectorants
- Cough syrup
- Nasal decongestant.
- Expectorant

2 .ORANGE PEEL



Fig no.2. ORANGE PEEL

Biological Sources :- The orange peel is the fresh or dried outer part of the pericarp of *Citrus aurantium* Linn.

family Rutaceae.

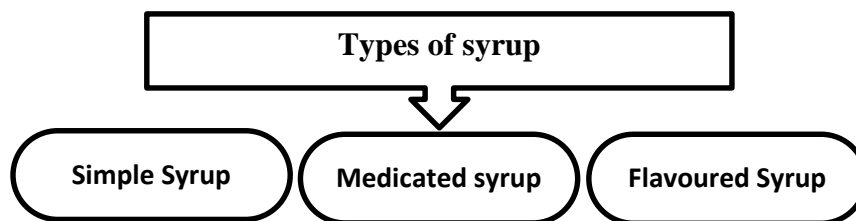
Chemical constituents : Gallic acid, caffeic acid, Ferulic acid, Lactic acid, Citric acid, Ascorbic acid (vitamin acid)

Uses:-

- To mask Bitter tastes
- Increase sweetness
- Fruity

- Chewy

TYPES OF SYRUP



Simple Syrup: When Purified Water alone is used in making the solution of sucrose, the preparation is known as " simple syrup," Simple syrup contains only sucrose (sugar) & Purified water.

Example: Sucrose :- 66.7ml Purified water:- 100ml

Medicated syrup : When Syrup contains medicinal substance is know as medicated cough syrup.

Example :-Ginger syrup Strong Ginger tincture5 mL Syrup q.s. 100 mL .

Flavoured Syrup : Syrups containing flavoring agents but not medicinal substances are called flavored vehicles; Containing Aromatic/ Flavoured - Flavoured syrup

Example: Cherry & Raspberry syrup.

PREPARATION OF EXTRACTS

1. Four Zingiber officinale were selected, their outer coats removed, and the resulting pieces were mixed to 100 millilitres of, which was thereafter slowly boiled to obtain extract. After filtering, the extract was allowed to cool. One millilitre of the entire extract is measured out.

2. To make extract, about 20g of peel from two oranges was chopped into small pieces and added to 100ml of water. The mixture was then boiled slowly. After filtering, the extract was allowed to cool. A 5 ml solution is measured from the entire extract.

3. To make extract, about 20 gm of Ginger rhizomes and orange peel were added to 100 ml of water and boiled gradually. After filtering, the extract was allowed to cool. A 5 ml solution is measured from the entire extract.

4. Precisely weigh 33.3 millilitres of sugar.

5. After combining all the extracts, 50 millilitres of syrup were produced.

6. After this syrup was prepared, it was put into an amber bottle, sealed, and kept in a cool place. Preparation of herbal syrup The simple syrup (66.7% w/v) was prepared as per Indian Pharmacopoeia. 200 mg of each extracts of Zingiber Officinale. and 400 mg of each extracts of Orange peel aromaticum ,Honeywere dissolved in simple syrup I.P. and the volume was made up to 100 ml and finally preservatives was added.

EVALUATION OF HERBAL COUGH SYRUP ^[23]

Physiochemical parameter likes specific gravity, density ,pH , refractive index, alcohol contain, acid value were analysed as per the standard procedure mentioned in Indian pharmacopoeia. The colour, odour, test were also recorded

| | |
|------------------|----------------|
| Colour | Greenish brown |
| Odour | Sweet aromatic |
| Test | Sweet |
| Specific gravity | 1.25 |
| Density | 1.37 |
| Refractive index | 1.54 |
| Alcohol contain | 0.81 |
| p ^H | 4.8 |
| Acid value | 0.118 |

COLOUR EXAMINATION

5 ml final syrup was taken into watch glasses and placed against white back ground in white tube light. It was observed for its colour by naked eye.

ODOUR EXAMINATION

2 ml of final syrup was smelled individually. The time interval among two smelling was kept 2 minutes to nullify the effect of previous smelling.

TASTE EXAMINATION

A pinch of final syrup was taken and examined for its taste on taste buds of the tongue.

DETERMINATION OF PH

Placed an accurately measured amount 10 ml of the final syrup in a 100 ml volumetric flask and made up the volume up to 100 ml with distilled water. The solution was sonicated for about 10 minutes. pH was measured with the help of digital pH meter.

RESULT AND DISCUSSION

The final formulation (F4) was obtained is stable than formulations F1, F2, F3. The formulation (F4) was obtained by minimizing the error in formulation F1, F2, F3. The formulation (F4) having antioxidant property hence it will be very helpful for researchers as well as industries to make the similar formulations on large scale.

| Sr. No. | Parameter | F1 | F2 | F3 | F4 |
|---------|------------------|----------|----------|----------|-----------|
| 1) | Density | 1.50gm. | 1.43 gm | 1.29gm | .. 1.50gm |
| 2) | Specific gravity | 0.6477 | 0.6575 | 0.6580 | 0.6581 |
| 3) | Viscosity | 3.81cp | 3.82cp | 3.62cp | 3.62cp |
| 4) | pH Determination | Neutral | Neutral | Neutral | Neutral |
| 5) | Colour | Reddish | Reddish | Reddish | Reddish |
| 6) | Odour | Aromatic | Aromatic | Aromatic | Aromatic |
| 7) | Taste | Sweet | Sweet | Sweet | Sweet |

CONCLUSION

Drugs like ginger have proven bronchodilator activity. rhizome of *Zingiber officinale* extract as traditionally used to manage cough. In the presence study rhizomes, Flower achieved therapeutic effect to relieve cough and reduced airway of inflammation. The pharmacological result also demonstrate that gingerols from *Zingiber officinale*. They effective in relieving cough due to presence of polyphenolic compounds especially flavonoids .cough is common in the population, yet the true prevalence of these condition remains difficult to define. Those based on good evidence are more likely to improve the clinical outcomes. The clinical and basic research studies are still needed for better diagnosis, treatment, prevention of cough in children or adults.

IN FUTURE SCOPE

In the upcoming years, it is anticipated that the cough syrup sector would continue to rise. The future of the industry will be shaped by important variables such product innovation, growing customer desire for healthier and natural options, and expanding uses in the food and beverage sector. The market for polyherbal cough syrup is expected to grow in the future due to the growing popularity of herbal and natural treatments for respiratory ailments. The fact that polyherbal cough syrup is a natural product without artificial ingredients that might have unfavourable side effects is one of its key benefits.

RESEARCH METHODOLOGY

To determine the primary studies, secondary sources, and guideline searches, the following sources were chosen: Medline (using the search engine PubMed) The Cochrane Library's Cochrane Database of Systematic Reviews, or EMBASE DARE stands for Database of Abstract of Reviews of Effects. The main Guideline Banks (LG) at Gruppo Italiano di Medicina Basata sulle Evidenze (GIMBE) have been identified. We used the following phrases to gather data from the PubMed (MeSH database) and Embase keyword registers: "Cough," "coughing," and "chronic," matched the terms "epidemiology," "prevalence," case-by-case in different search strings. "Incidence, cause, diagnosis, outcome, and treatment" We searched for specific clinical regions in PubMed using the clinical queries search engine and the pre-defined phrase "chronic cough children. The domains of aetiology, diagnosis, prognosis, and therapy, as well as any existing "clinical prediction guides," might all be independently investigated. We searched the literature for our findings without setting a deadline, and we finished on September 8, 2014. The selection was further limited to reports having human subjects between the ages of 0 and 18 that were written in either English or Italian. We restricted our search to randomised controlled trials (RCTs) while looking for literature about

therapy. We did not include non-systematic reviews, editorials, letters, works of pure study, or grey literature in our investigation.

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