Efficacy and safety of herbal medicines for relief cough symptom in national list of essential medicines of Thailand and Lao PDR: A systematic review and Meta-analysis

Ladda Her

A Thesis Submitted in Partial Fulfillment of Requirements for

degree of Master of Pharmacy in Clinical Pharmacy

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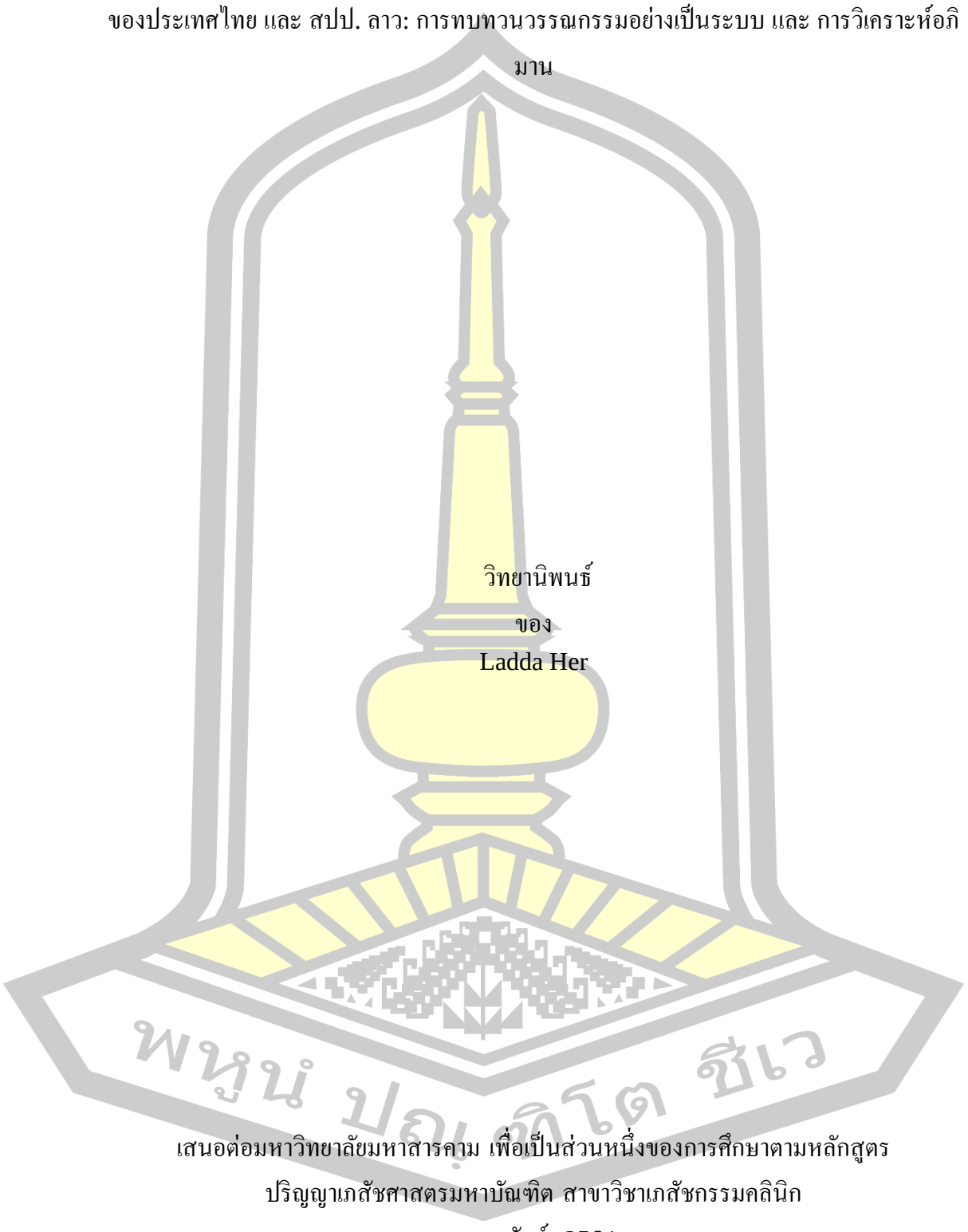
ประสิทธิผล และ ความปลอดภัยของยาสมุนไพรสำหรับบรรเทาอาการไอในบัญชียาหลักแห่งชาติของประเทศไทย และ สปป. ลาว: การทบทวนวรรณกรรมอย่างเป็นระบบ และ การวิเคราะห์อภิมาน



วิทยานิพนธ์

ของ

Ladda Her

เสนอต่อมหาวิทยาลัยมหาสารคาม เพื่อเป็นส่วนหนึ่งของการศึกษาตามหลักสูตร

ปริญญาเภสัชศาสตรมหาบัณฑิต สาขาวิชาเภสัชกรรมคลินิก

กุมภาพันธ์ 2564

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The examining committee has unanimously approved this Thesis, submitted by Ms. Ladda Her , as a partial fulfillment of the requirements for the Master of Pharmacy Clinical Pharmacy at Mahasarakham University

Examining Committee

.....Chairman
(Asst. Prof. Peeraya Sriphong , Ph.D.)

.....Advisor
(Asst. Prof. Juntip Kanjanasilp , Ph.D.)

.....Co-advisor
(Asst. Prof. Ratree Sawangjit , Ph.D.)

.....Committee
(Asst. Prof. Somsak Nualkaew , Ph.D.)

.....External Committee
(Assoc. Prof. Sunee Lertsinudom , Ph.D.)

Mahasarakham University has granted approval to accept this Thesis as a partial fulfillment of the requirements for the Master of Pharmacy Clinical Pharmacy

.....
(Asst. Prof. Chanuttha Ploylearmsang , Ph.D.)
Dean of The Faculty of Pharmacy

.....
(Assoc. Prof. Krit Chaimoon , Ph.D.)
Dean of Graduate School

TITLE Efficacy and safety of herbal medicines for relief cough symptom in national list of essential medicines of Thailand and Lao PDR: A systematic review and Meta-analysis

AUTHOR Ladda Her

ADVISORS Assistant Professor Juntip Kanjanasilp , Ph.D.

Assistant Professor Ratree Sawangjit , Ph.D.

DEGREE Master of Pharmacy **MAJOR** Clinical Pharmacy

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ABSTRACT

Introduction: cough is the common symptom of the respiratory tract infections or non-infections, the duration of cough indicates a classification and severity of the disease. Herbal medicines can be used as the alternative to drugs for relief of cough symptoms from acute and chronic disease. herbs were used for reducing cough but lack of evidence to confirm their efficacy and safety. The present study aims to evaluate the efficacy and safety of herbal medicines for the relief of cough symptom in the national essential drug list of Thailand and Lao PDR.

Method*:* the studies were searched in the Cochrane Library, PubMed, Scopus, CINAHL, Springer, Science Direct, ProQuest, and THAILIS databases. we searched from its inception until 01/02/2019 for randomized control trials. We followed for the efficacy and safety of herbs for reducing cough. Methodological quality was evaluated by using the Cochrane risk of bias tool; two reviewers in our team screened eligibility and extracted data.

Result*:* Twenty studies were included for the review and seventeen studies were included in the meta-analysis, there were 4,098 persons and age between 1 and 80 years old. Four herbs in the studies including eucalyptus (n: 6), honey (n: 10), ginger (n: 3) and Malabar nut (n: 2) studies. Overall of the risk of bias included trial, we found poor in missing outcome data. Ten of 20 included study were the effect on cough in children and eleven studies in adult. All four herbs were used as a pure herb (n: 7) and in combination with mixture herbs (n: 14). All of the studies with herbs were compared for efficacy and safety with placebo or standard treatment. Dosage form in studies included syrup (n:11), capsules (n: 9), and spray (n:1). Most of the included studies found that eucalyptus and honey, ginger, and mabala-based preparations were superior to placebo and no difference with active control in reducing cough symptom and improve quality of life. This meta-analysis supports these findings and shows that eucalyptus reduce overall cough score small heterogeneity (I^2 = 1.2%, $\chi 2$ = 1.01; P-value = 0.314). The efficacy of eucalyptus was found a statistically significant (n = 402, RR: 1.40, 95%CI [1.19, 1.65], P-value < 0.0001) when compared with placebo. The effect of honey compared

placebo statistic significantly in all cough symptom (n = 3252, SMD: -0.63, 95%CI [-0.85 to -0.40], I^2 =0 %, P<0.0001). Honey compared active control or standard treatment the data shown overall effective of cough statistic no significant all studies included P=0.07 (n=3111, SMD: -0.29, 95%CI [-0.60 to 0.02], I^2 =93 %, P<0.0001). Ginger and malabar nut were good effects for cough symptom URI, COPD and asthma. however, these herbs will need evidence to support this respect. The AES showed no statistic difference between treatment and control group.

Conclusion: This review found four herbs from 30 herbs essential national drug list in Thailand and Lao PDR including eucalyptus, honey, ginger, and malabar nut. Eucalyptus and honey were positive effects than placebo in alleviating the overall symptom of patients' cough and improved patient quality of life. The better positive effect when we compared with standard treatment was found a similar effect. We suggest this herbal medicine may be recommended as an adjunct to conventional medicine. The effect reduces cough symptom of ginger and malabar nut will need evidence to support this respect. Additional research, including other herbal treatments, is needed in this area.

Keyword : Eucalyptus, Honey, ginger, justicia, Malabar nut, systematic review, meta-analysis

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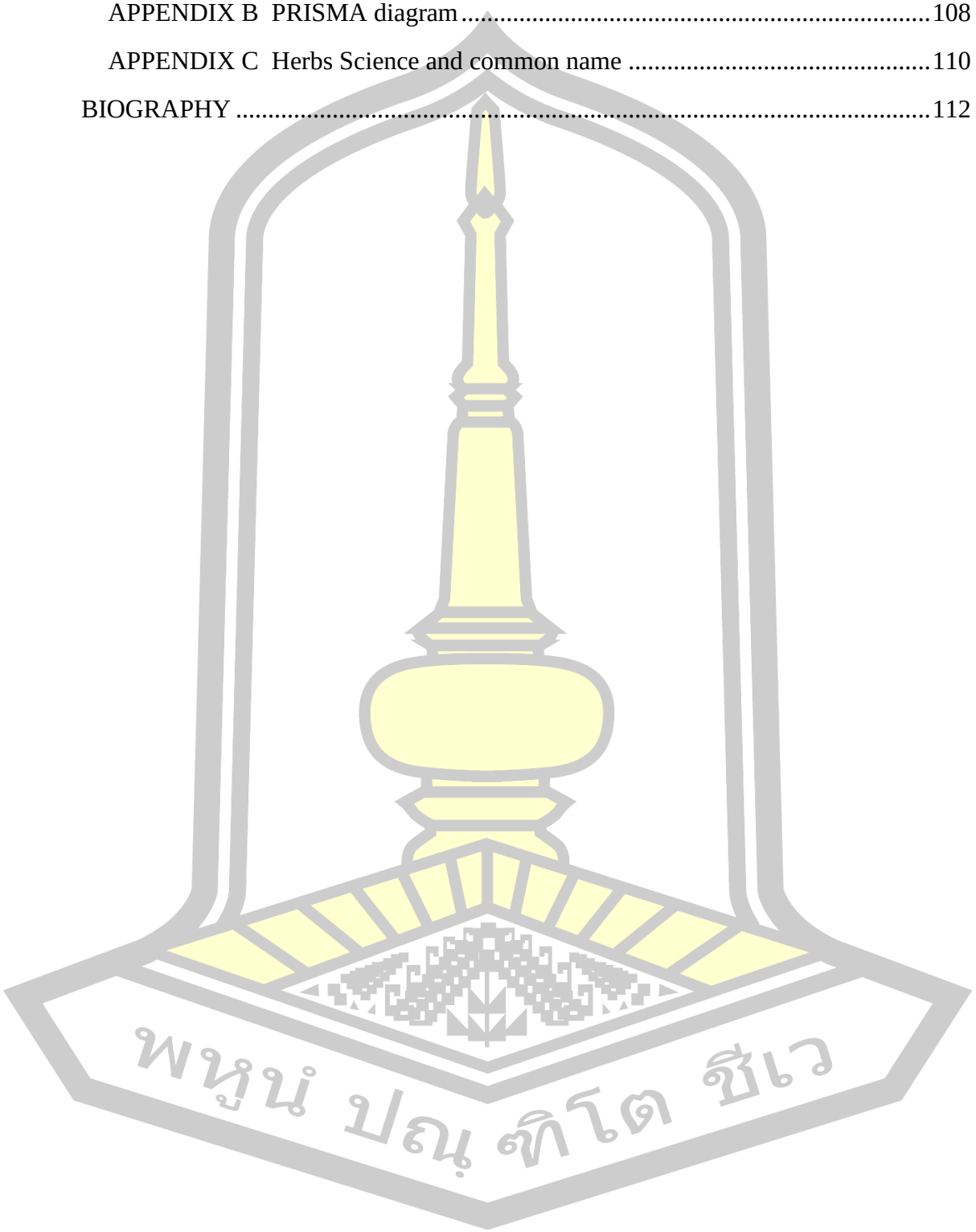

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CHAPTER 1
INTRODUCTION

1.1 Background

Cough is the commonest reason present in patients with respiratory tract infection and visit in a primary care. Patients in the United States made an estimated 1.2 billion visits to physician offices and hospital outpatient departments (OPDs) and emergency department (EDs) (1); leading to high expense of treatment. In addition, chronic cough leads to reduce patient of quality of life. The epidemiology of cough can diagnostic from cause of cough: acute cough is ordinarily a result about cause from viral and bacterial upper respiratory tract infection and is often resolve following clearance of the infection(2), and chronic cough is a cause of a number of chronic respiratory diseases such as COPD, asthma, and idiopathic pulmonary fibrosis.(3, 4).

Survey of patient health in Government-generate statistics from Australia(5) and the United States (6) reveal that cough of undifferentiated duration is the single most common complaint for which patients of all ages seek medical care from physicians in the primary care setting in year 2014-2016. Further, medicinal costs for cough and cold remedy products in the over-the-counter market are high approximately $6.8 billion dollar in the United States and $156 million in Great Britain since 2013. While these countrywide figures are large, especially in the United States, they greatly underestimate the total cost of treating cough. They do not reflect the total economic burden of direct costs that include the physician fees, radiographs, and laboratory testing, and the cost of prescription drugs for the myriad causes of cough other than the common cold and indirect costs, such as time missed from work (7).

The pathophysiologic basis of the cough reflex has been better characterized by the use of inhalational challenge tests in human subjects with chemicals such as capsaicin, chloride-deficient solutions, citric acid, and prostaglandins (8). So, coughing is an important defensive reflex that enhances clearance of secretions and particulates from the airways and protects from aspiration of foreign materials occurring as a consequence of aspiration or inhalation of particulate matter,

pathogens, accumulated secretions, postnasal drip, inflammation, and mediators associate with inflammation (9).

Currently, there are more evidences to suggestion for cough classification by chest guideline recommendation class following by duration of cough symptom including: cough less than 3 weeks suggest is acute cough, cough duration between 3-8 weeks is subacute cough and finally cough symptom present more than 8 weeks is chronic cough. Moreover, physician are finding causes of cough to support within cough duration (10). Among these types of cough, acute cough or acute bronchitis is the single most common cause of consultation (11), and presentations in general practice. In Australia and USA, acute cough is the fifth most common new presentation to ambulatory care with 10 ambulatory visits per 1000 visits each year, while in the United Kingdom there are about 50 cases per 1000 people each year. The morbidity surveys shows that the overwhelming majority of acute coughs are infectious (12). The chronic cough is a major cause of morbidity being reported by 3–40% of the population. A European Respiratory Society-supported survey of 18,277 patient subjects age between 20 - 48 year from 16 countries worldwide report nocturnal cough in 30%, productive cough in 10%, and non-productive cough in 10%(13). There are wide variations in the report incidence of the three common causes of cough illustrated. This reflect is differences in the population and in the strategy for establishing a diagnosis. Either a battery of tests may be employed or alternatively a therapeutic trial with reduction in cough taken as indicating an etiologic (14).

Several therapeutic options for cough have been used for relief or remedy used for other symptoms and increase patient quality of life including pharmacotherapies such as cough suppressants, expectorants, and mucolytic, non-pharmacotherapies(15) and natural herbal medicines (16).

So anyway, cough medication products are commonly using in primary care in the world wide, although most country spend more of money and not strong evidences to support their efficacy and safety. However the alternative treatment such as herbs are better to choose and has long history in the world wide for remedies of this symptom.

Currently, publication report of use herbs for reduce symptom of respiratory tract infection and supporting to modifier and development by use pure product to herbal medicines and show effectiveness in study by ethnobotany and commercial history of plant extract (17-19).

Asian peoples, particularly Southeast and South Asian, are very fond of herbs. The Asian traditions of using herbs are based on centuries of trial and error, most herbs can be used to cure human ailments and also alternative therapies for healing. In fact, the term ‘herb’ is often understood by most laymen as ‘medicinal plants’. Most country in this area such as Thailand and Lao have long traditional culture ago with history of nature products use such as natural plants for relief cough symptom. For herbs formula use in this location have more than 30 species came to use for reduce patient within cough symptom. Currently, there are research trials on alternative herbal medicines and increase using herbs came to reduce cough symptom. However all herbs do not have enough of evidences to support their efficacy and safety in human. So in this study, we interest to find clinical trial of herb used for relief cough and will use systematic review for conclude of any trial on database and total result all trial by using meta-analysis.

1.2 Question research

How are the efficacy and safety of Thai and Lao herbal medicines for relief cough symptom?

1.3 Objective

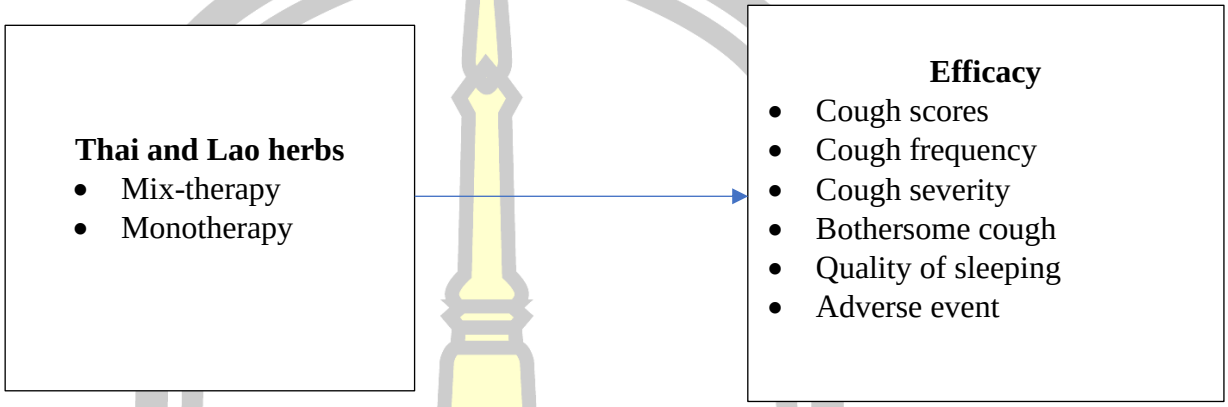
To determine the efficacy and safety of Thai and Lao herbal medicines for relieving cough.

1.4 Scope of the research

In this study we will use systematic review and meta-analysis to summary evidences of herbal medicine for relieve cough symptom. In addition, we will include

all research articles in human. We conduct of Thai and Lao herbs by review form both country nation list of essential medicine.

1.5 Conceptual framework



1.6 Specific definition

- Cough is a symptom present in respiratory system include upper and lower respiratory, infection and non-infection.
- Type of cough are focus all types include acute cough, sub-acute cough, and chronic cough, moreover we will include productive cough and non-productive cough.
- Herbal medicines are products from natural plant and animals or pure extract from all the part of natural plant including flower, fruit, leave, and root.
- Plant extract in all dosage form such as oil, syrup, or powder have modified to mix herb or one of herb in formula.
- Efficacy mean the effect of reduce symptoms such as cough score, frequency, severity, bothersome of cough, and quality of sleeping all night.
- Safety are adverse event after receive herbal medicines including minor or major events.
- GI symptom are
- Adult are patient who have age more than and equal to 18 years old.
- Children are patient who have age less than 18 years old.

1.7 Expected Benefits

- To evaluate and support alternative treatment for relief cough symptom in this area.
- To reduce modern medicine use and reduce cost for relief cough symptom.
- To show efficacy and adverse events of herb for remedies cough symptom as the information for selection the herbs to national drug lists.

CHAPTER 2
LITERATURE REVIEW

2.1 Cough epidemiology

In epidemiology of cough survey from the word wide and definition for cough are a common cause of respiratory disease such as: common cold, asthma, COPD, pneumonia and respiratory infections. A cough is a reflex that helps patient body clear throat and lungs, In addition, it is common in patient who have disease about respiratory infection or non-infection. About cough symptom was present by common reflex action that clears the throat of mucus or foreign irritants. Coughing to clear the throat is typically an infrequent action included shortness of breath, wheezing or a whistling breathing, runny nose, sore throat, heartburn, weight loss, night sweats, difficulty swallowing or coughing when swallowing (20).

Cough is the commonest symptom leading in patients to consult with the physician. Whether it is the commonest medical products of all depends on whether other symptoms such as hunger and thirst may be counted as physiological. In a few subjects, chronic cough leads to a profound loss of quality of life. The epidemiology of cough can be neatly divided into these two diagnostic subgroups: acute cough, which is usually due to viral respiratory tract infection, and chronic cough, which may be arbitrarily defined as cough lasting longer than eight weeks (16).

Acute cough is the single most common cause of consultation. The prevalence of chronic cough, arbitrarily defined here as a cough of >8 weeks duration, is difficult to estimate since response rates vary according to the question posed. There is no doubt that chronic cough is a major cause of morbidity being reported by 3 - 40% of the population. A European Respiratory Society-supported survey of 18,277 subjects aged 20 - 48 from 16 countries worldwide reported nocturnal cough in 30%, productive cough in 10% and non-productive cough in 10% (21).

2.2 Definition of cough

Acute cough is defined as one lasting less than 3 weeks and an acute cough is normally benign and self-limiting. Moreover, acute cough is the commonest new presentation in primary care and is most commonly associated with viral upper respiratory tract infection and commonest symptom associated with acute exacerbations and hospitalisations with asthma and COPD (22).

Chronic cough is presented a challenge for the clinician. Typically defined as a cough that persists for longer than 8 weeks, this is the most common presenting symptom in adults who seek medical treatment in an ambulatory setting and estimate to occur in up to 40% of the population. Chronic cough was understood to be a consequence of several diseases affecting airway sensory nerve terminals, such as rhinitis, gastroesophageal acid reflux, and eosinophilic airway diseases (23).

2.3 Pathophysiology of cough

Understanding of the cough response and of how cough may become persistent is of the utmost importance. The anatomy of the cough reflex has been dissected extensively, with a central pathway and efferent pathways defined. The cough reflex is sub served mainly by vagal primary afferent nerves such as bronchopulmonary rapidly adapting receptors (RARs) which can be evoked by mechanical stimulation and deformation of the airway epithelium such as particulate matter or mucus, and by airway smooth muscle contraction induced by constrictor agents (24).

The human cough reflex is still poorly understood, although it is known to occur independently of bronchoconstriction. Sensitization of the cough reflex is a unifying hypothesis for chronic dry cough in several conditions, including gastroesophageal acid reflux, angiotensin-converting enzyme inhibitor cough, and cough-variant asthma. The most common cause of chronic dry cough is a group of related conditions of chronic rhinitis, sinusitis, and postnasal drip. In these cases the cough reflex may be sensitized through an action of inflammatory mediators from the nasal mucosa on the airways or a reflex sensitization of airway sensory nerves (25).

2.4 Cough classification

Coughing is a symptom and can form into group or classifies by its duration (how long it lasts) and by other specific features

Acute cough: symptom are sudden onset and lasts up to 3 weeks.

Sub-acute cough: present in lasts between 3-8 weeks.

Chronic cough: present lasts for more than 8 weeks.

Currently, information from evidence can descried for type of cough follow by symptom and causes.

Productive cough: Cough than brings up phlegm.

Dry cough: Cough that does not bring up phlegm.

Nocturnal cough: Cough that only happens at night.

Hemoptysis: Coughing with blood.

2.5 Causes of acute or short-term cough

Upper respiratory tract infections (or URTIs): This is the most common cause of acute cough. URTIs are infections of the throat and almost always caused by viruses. They are usually associated with fevers, sore throat and runny nose. This group includes the common cold, viral laryngitis and influenza. Whooping cough is a highly contagious respiratory infection that produces a cough that makes a high-pitched “whoop” sound (26).

Hay fever (or allergic rhinitis): This common allergic condition can mimic the symptoms of a common cold. It is usually associated with dry cough, sneezing and runny nose. There is usually an allergy trigger in the environment (27).

Inhalation of irritants: Acute exposure to some fumes and vapour can cause inflammation of the throat and airway and cause cough. Inhaler are substances may affect respiratory system from this factor, such as the characteristics of substances, environment and host factors, and sometimes can be absorbed into systemic circulation, causing toxicity to various organ systems (28, 29)

Lower respiratory tract infections (or LRTIs) or Pertussis: These are infections of the airways below the throat that usually cause cough and fevers. So, Pertussis causes an acute cough that can often become persistent and is classically associated with paroxysms of coughing, inspiratory whooping, and post-tussive vomiting. They can affect the airways (bronchitis) or go further into the lungs (pneumonia) (26).

Lung clot (or pulmonary embolism): This is a potentially life-threatening condition where blood clots travel, usually from leg veins, to the lungs causing sudden shortness of breath and sometimes coughing (30).

Lung collapse (or pneumothorax): This is caused by the deflation of the lung. It can be spontaneous or due to chest trauma. More commonly seen in smokers with history of emphysema (air pockets within the lungs), signs of lung collapse include sudden chest pain, dry cough and shortness of breath (31).

Post-nasal drip (or upper airway cough syndrome): This condition shows up as dry cough caused by the chronic dripping of mucus from the back of the nose to the throat. Usually this occurs after a recent infection or continuous exposure to an allergy trigger (32).

Gastro-oesophageal reflux (or GERD): This is also commonly known as acid reflux disease. The acid within the stomach backs its way up to the oesophagus. It can potentially leak into the throat causing irritation and dry cough. It is usually associated with heartburn (33).

2.6 Cause of chronic cough

Some causes of chronic cough include:

COPD: The airway and lungs are inflamed, which causes chronic cough with phlegm and shortness of breath.

Asthma: Asthma can cause sporadic dry cough. This could be a sign that your asthma is not fully controlled. Sometimes cough only happens in specific locations such as the workplace or school.

Medications: ACE inhibitors (medications for elevated blood pressure), can cause dry cough.

Chronic lung infections: Some lung infections can cause chronic cough. Tuberculosis, a highly contagious lung infection, can cause fevers, night sweats and cough, sometimes had phlegm with blood.

Lung cancer: cancer originating in the lung or spread from other organs can cause cough, sometimes with blood (13, 34).

This enormous morbidity is cause by a wide array of viral pathogens including influenza, Para influenza, rhinovirus, adenovirus, respiratory syncytial virus and the respiratory corona virus. All of these viruses share a common short incubation period of between 1 and 4 days. Because of its ability to undergo antigenic shift and genetic recombination influenza occurs in epidemics. Why these epidemics occur during the winter months is unknown but may be related to cooling of the airway epithelium decreasing host defences. Para influenza viruses differ from influenza viruses in that they are much more antigenic stable and of the four sub-types one and three are particularly important, causing serious lower respiratory tract infections, croup and trachea bronchitis in infants and young children. In all, Para influenza viruses are thought to be responsible for a fifth of all non-bacterial respiratory tract disease in childhood. Since immunity to reinfection was only transient it is one of the commonest causes of the typical infective cough which plagues families with small children (35).

2.7 Diagnosis

2.7.1 Acute cough

Cough is the most common complaint for which patients visit their primary care physician, being present in about 8% of consultations. The history and clinical findings are compatible with cold or bronchitis, neither a chest radiograph nor clinical chemistry is necessary, provided there are no danger signs. It is not necessary to distinguish between viral and bacterial bronchitis by determination of leukocytes or C-reactive protein (CRP), because the findings have no consequences for treatment. The colour of the sputum has no predictive value for the diagnosis of bacterial bronchitis or the differentiation between pneumonia and bronchitis. Sputum examination in an otherwise healthy bronchitis patient is pointless, because antibiotics

are not required. Spirometer is indicated in the presence of signs of bronchial obstruction, because acute bronchitis can cause temporary airway constriction. A patient whose cough persists should be investigated in more detail after no more than 8 weeks (36).

2.7.2 Chronic cough

Chronic cough has been defined as one lasting more than 8 weeks, although a cough following an upper and lower respiratory tract infection may persist for considerably longer. It is therefore more satisfactory to define chronic cough as one lasting more than 8 weeks and to recognize an overlap period of 3 - 8 weeks. Using a combination of history, physical examination, and laboratory investigations directed at these sites, possible causes for the cough were considered TB, respiratory disease such as asthma, pneumonia, postnasal drip. The suspected cause could then be confirmed if the cough resolved or significantly improved after a trial of diagnosis specific treatment (37, 38).

2.8 Cough management

Patients with cough frequently are present to clinicians working in both primary and secondary care. Acute cough, which often follows an upper respiratory tract infection, may be initially disruptive but is usually self-limiting and rarely needs significant medical intervention (22).

Symptomatic treatment for cough symptom

Causal treatment should always be sought. However, if this approach is impossible (e.g. acute viral respiratory infection) or would only prove effective in a delayed manner (e.g. tuberculosis), symptomatic treatment can be considered instead of, or complementary to, causal treatment of cough. Symptomatic treatment targets one or several of the five parts of the cough reflex arc. Effects can be protussive (increasing cough and expectoration) or antitussive.

Herbal medicine of cough

Despite being clinical routine in both hospital and outpatient care had treatment for cough symptom such as pharmacotherapy, physiotherapy and natural herb medicine, as well as in rehabilitation, evidence for the efficacy of all treatments choice for reduce cough is lacking.

- Increase expectoration using effective coughing techniques for patients with productive but ineffective cough.
- Suppress voluntarily non-productive cough.
- Instruct patient in the use of physiotherapeutic equipment improving expectoration

Pharmacotherapy:

The actions of complementary and alternative medicines (CAMs) in the treatment of cough and of the conditions associated. Pure chemicals can be extracted from many of the herbs used as antitussives, and can be shown to be effective in randomized, blind, and controlled trials, but it does not follow that the herb itself, used in the recommended formula and shown to be antitussive, acts by this agency unless a placebo effect is ruled out. A few herbs are identified where the evidence points to a true antitussive action (39).

Productive cough:

This cough is a reflex triggered when the body senses that some kind of irritating substance is present in the airways or lungs. In the case of productive cough symptoms, that irritating substance is mucus, and the cough clears mucus out of the body.

The mucus may be thick or thin and can be a variety of colours. Depending on the cause, a productive cough can last only a few days or weeks or can continue for months to years.

Associated productive cough symptoms include:

Pain in the chest when coughing

Clear, grey, yellow, or green mucus

Bloody mucus

Difficulty breathing

Fever or chills

Tiredness

Weight loss

Nasal congestion

Productive Cough Causes Overview

A productive cough is commonly caused by an infection, which can range from mild to serious. It can also be caused by an underlying medical condition or a blockage of the airways (40).

Mechanical productive cough causes:

The presence of a structure blocking the airways can cause a build-up of mucus, resulting in productive cough symptoms. This can occur with cancer (less common cause) or a foreign body, particularly in children.

Infections:

The body responds to infections by producing mucus, which traps invading bacteria and viruses and triggers coughing so that they can be cleared.

Viral infections: A viral infection of the upper airways or the lungs can lead to a productive cough. Mucus produced in the airways can be coughed up, or mucus from the nose and sinuses can drip down the back of the throat, triggering a cough. The common cold and acute bronchitis are examples of infections that are typically viral.

Bacterial infections: These are usually more severe than viral infections. Depending on the specific type of infection, they may be associated with high fever, chills, difficulty breathing, and coughing up blood. Tuberculosis is one example of a bacterial infection of the lungs that causes a productive cough.

Chronic respiratory diseases: Underlying diseases of the respiratory system can cause lasting structural changes that contribute to chronic productive cough symptoms.

Smoking damage: The effects of smoking over time can damage the airways, causing difficulty breathing along with a productive cough.

Airway inflammation: Recurring inflammation in the airways can contribute to overproduction of mucus. Bronchiectasis is one example of an inflammatory condition that can lead to excess mucus and a productive cough.

Bronchiectasis is defined as the "irreversible abnormal dilatation of the bronchi". It is a common cause of chronic productive cough which is diagnosed by a high resolution CT (HRCT) scan demonstrating a bronchus with an internal diameter wider than its adjacent pulmonary artery which fails to taper and bronchi visualized 1-2 cm from the pleural surface (41)

Broad principles in the management of the condition include treatment of the underlying cause, monitoring of disease activity using lung function and regular sputum cultures, airway clearance techniques and antibiotic treatment (42)

Chronic bronchitis is defined as "the presence of a chronic productive cough for more than 3 months in 2 successive years". It is almost invariably described as a feature of Chronic Obstructive Pulmonary Disease (COPD) secondary to smoking (43).

Treatment for productive cough

Treatment of chronic bronchitis is largely based on treatment of the underlying COPD, as per NICE COPD guidelines. Certain treatment considerations that may particularly apply to patients with chronic bronchitis include the use of mucolytic therapy and judicious use of antibiotic therapy based on sputum colour and culture results. Another promising emerging treatment (44).

Mucolytic therapy

Mucolytic agents are widely prescribed to patients with chronic bronchitis in an attempt to improve their symptoms related to sputum production. The evidence for their use is mixed although a 2012 Cochrane review concluded that they may produce a small reduction in the exacerbation rate of patients with chronic bronchitis and COPD albeit with no difference in quality of life.(45)

Antibiotics

It is generally accepted that for subjects with chronic bronchitis a change in the amount or nature of sputum produced, beyond day-to-day variation, may signify an exacerbation and the production of green (purulent) sputum has been found to be highly sensitive (94.4%) and specific (77%) for the yield of a high bacterial sputum load. Guidelines therefore recommend antibiotic treatment following change in sputum quantity or quality (46).

Roflumilast

A phosphodiesterase 4 inhibitor which has anti-inflammatory effects in the airways by preventing the breakdown of intracellular cyclic AMP, a substance that when degraded leads to the release of inflammatory mediators (47, 48).

Non-productive cough

A dry cough is a cough where no phlegm or mucus is produced (known as non-productive). A dry cough is irritating and usually associated with a tickly throat. Dry coughs are often caused by viral illnesses such as colds and flu, but they can also be caused by allergies or throat irritants (49)

Causes of dry cough

A dry cough is often the result of: a viral illness, such as a cold or influenza (the flu); or a post-viral, or post-infective, cough (cough that persists for weeks after a viral illness). however, a dry cough may be a result of other problems, such as: asthma; gastro-oesophageal reflux; smoking; allergic rhinitis (hay fever) due to inhaling substances patient are allergic to such as pollen, dust or pet dander; post-nasal drip (the drainage of mucus secretions from the nose or sinuses down the back of the throat - also known as upper airway cough syndrome); laryngitis (inflammation of the larynx, also known as the voice box); whooping cough; obstructive sleep apnoea and snoring; habit cough (a cough that is only present in the daytime and not caused by illness – it most often affects school-aged children); an inhaled foreign body (e.g. food or other objects accidently being inhaled - usually in babies and small children); certain types of lung disease known as interstitial lung disease; or a side effect from a medicine (for example, cough is a possible side effect of most ACE inhibitors often prescribed for high blood pressure).

Other, less common, causes of a dry cough include: heart failure; pulmonary embolism (a blood clot in the lungs); or lung cancer.

A dry cough can be aggravated by: breathing cold, dry air; air pollution; inhaled irritants such as dust or smoke; exposure to tobacco smoke; excessive use of your voice; or a change in temperature and specific treatment for a dry cough will depend on the cause of the cough (22).

Treatment of non-productive cough

Symptomatic relief must be considered when the cough interferes with the patient's daily activities and this is effectively treated with antitussive preparations which are available as combinations of codeine or dextromethorphan with antihistamines, decongestants and expectorant, antitussives are used for effective symptomatic relief of dry or non-productive cough. First generation antihistamine like chlorpheniramine and centrally acting opioid derivatives like codeine are often used alone or in combination in the management of nonspecific cough. Sedation caused by

these is valuable, particularly if the cough is disturbing the sleep. Although there is extensive experimental data on single agent antitussives and antitussive combinations, there is a major paucity of published literature on these combinations in nonspecific cough. Treatment of dry cough remains a challenge in some patients and this article reviews the scope of the current drugs and combination of Codeine and Chlorpheniramine in the effective management of dry cough (50).

Antitussive drug

Morphine is an effective antitussive at doses lower than those that produce analgesia and sedation. It is not commonly used for antitussive activity because of adverse effects and the potential for abuse and addiction. Morphine has poor oral bioavailability due to a significant first-pass effect by the liver (51).

Codeine is methyl-morphine; methylation of morphine significantly improves the oral bioavailability by reducing the first-pass effect. Codeine phosphate and codeine sulphate are found in many preparations, including tablets, liquids, and syrups. Codeine has analgesic effects that are about one-tenth that of morphine, but its antitussive potency is about equal to that of morphine.

Mechanism of Action: the physiological mechanism of cough is complex, and little is known about the specific mechanism of action of the opioid antitussive drugs and the receptors involved appear to be different than those involved with the other actions of opioids

It is likely that both central & peripheral effects may play a role

The adverse effects of codeine are significantly less than those seen with morphine at antitussive doses. Toxicity (especially in cats) is exhibited as excitement, muscular spasms, convulsions, respiratory depression, sedation, and constipation. Codeine should not be used after GI tract surgery because of its effects on intestinal motility. The potential for addiction and abuse of codeine is considerably lower than that for morphine

Hydrocodone is chemically and pharmacologically similar to codeine but more potent. It is combined with an anticholinergic drug (homatropine) to discourage abuse by people.

Dextromethorphan is technically not considered an opiate, because it does not bind to traditional opiate receptors and is not addictive or analgesic. It is the d-isomer of levorphanol. The l-isomer of levorphanol has addictive and analgesic properties. Although it is recommended anecdotally to treat cough, a pharmacokinetic study in dogs demonstrated a short elimination half-life, rapid clearance, and poor oral bioavailability, making its use as an orally administered cough suppressant in dogs questionable.

Mechanism of Action:

Opioid derivative, decreases the sensitivity of cough receptors interrupts the transmission of cough impulses by depressing the medullary cough centre through sigma receptor stimulation, also combined with promethazine or other decongestants in some formulations for reducing cough and cold symptoms
Dextromethorphan is well absorbed from the gastrointestinal tract, with maximum dextromethorphan plasma concentrations occurring 1 - 4 hours after oral administration in extensive metabolizers and 4 - 8 hours after oral administration in poor metabolizers. Dextromethorphan has a plasma elimination half-life of 1 - 4 hours in extensive metabolizers and 17-42 hours in poor metabolizer subjects (52).

Butorphanol,

An opioid agonist-antagonist, is used as an analgesic and antitussive in dogs. As an antitussive in dogs, butorphanol is 4 times more potent than morphine and 100 times more potent than codeine. At antitussive dosages, it may produce considerable sedation in dogs. Because butorphanol has poor bioavailability, the oral dose in dogs is 10 times the SC dose. In cats, butorphanol is primarily used as an injectable analgesic. In some cats, it may cause pain on injection, as well as mydriasis, disorientation, swallowing/licking, and sedation.

Local Anesthetics

Local anesthetics have been reported to have antitussive effects and, given the involvement of sensory nerves in the cough reflex, it is perhaps not surprising that local anesthetics can inhibit both experimentally induced cough as well as cough in a variety of clinical circumstances. This antitussive activity is presumably due to the ability of local anesthetics to block Na V+ channels in sensory nerves (53).

Benzonatate

A long chain polyglycol derivative chemically related to procaine, is a peripherally-acting, oral anesthetic agent whose mechanism of cough suppression is believed to involve inhibition of pulmonary stretch receptors. Studies performed soon after its approval in the United States a half century ago showed benzonatate able to inhibit experimentally-induced cough as well as to suppress subjectively-measured pathological cough (52).

2.9 Adverse event of medicines product for remedy cough symptom

From pharmacology review article on 2014 were reported about safety of over the counter drugs for remedies cough symptom included: GI symptom, CNS symptom when patient given overdose, about drug interaction of antitussive has limited of research or report such as the information from review research in brazil about efficacy and safety of over the counter register in brazil, the author report was objective of study was to analyse the level of evidence regarding the efficacy, effectiveness and safety of over-the-counter (OTC) cough medications registered in Brazil. The National Health Surveillance Agency database was used to identify the drugs. Clinical trials, systematic reviews, meta-analyses, and studies on safety were searched on the Medline baseline, the Cochrane Library and SIETES (System of Essential Information in Therapeutics and Health; database in Spanish). Most drugs (62.5%) were sold as a fixed-dose combination of two or more drugs. Randomized clinical trials were found for only three drugs: bromhexine, dextromethorphan and

guaifenesin. No clinical trials were found for fixed-dose combinations. Systematic reviews on Cochrane did not report any evidence in favour of or against the effectiveness of cough drugs. Efficacy is also unclear, especially regarding fixed-dose combinations. The evidence for the efficacy of OTC cough medications available in Brazil is poor due to the lack of quality studies. Pharmacovigilance of OTC cough medications should be encouraged (54).

From feasibility Study they shown the evidences about safety of over the counter cough medicines include combinations of antihistamines, decongestants, antitussives and expectorants. Systematic reviews show no evidence these products are of benefit compared to placebo. Despite this the UK market for these products in 2009 was worth £ 437.2 million.

There have been multiple reports of adverse effects associated with cough medicines. In children under 6 years of age decongestants have been linked to cardiac arrhythmias, antihistamines to hallucinations, and antitussives to depressed levels of consciousness and encephalopathy. Hospital episode statistics for England 2006/7 showed 230 children under 14 were admitted to hospital as a consequence of exposure to antitussives, expectorants or common cold remedies (11 poisoning by antitussives, 39 poisoning by expectorants, 182 poisoning by common cold remedies). The USA the Food and Drug administration identified 123 deaths related to the use of such products (55).

2.10 Alternative treatment for remedies cough symptom

Pure chemicals can be extracted from many of the herbs used as antitussives, and can be shown to be effective in randomized, blind, and controlled trials.

Natural methods of treatment are most effective as they provide quick relief at practically no cost. More importantly, they pose little to no risk of side effects. But before patient dive into those natural dry cough remedies, let’s take a quick look at the symptoms and possible implications to rule out anything more serious.

From any research shown importance evidence of used plant in remedy cough symptom such as the review article from Korea plant, Traditional plant-based therapies for respiratory diseases found in North Jeolla Province, Korea shown 14

respiratory diseases have been treated with a total of 43 species of medicinal plants belonging to 40 kinds in 26 families. This study also reported 149 different modes of plant-based therapeutic application of medicinal material. The informant consensus factor for the common cold is 0.84, the highest among 14 different respiratory ailments, followed by whooping cough, asthma, nosebleed, bronchitis, cough, and so on. Medicinal plants used to treat seven respiratory ailments had a 100% fidelity level and can help to preserve the traditional knowledge and local health traditions of North Jeolla Province amid rapid industrialization and urbanization.

The findings of this study warrant follow-up clinical research to determine the most effective traditional remedies toward development of herbal medicinal products for integration into the Korean health care system (56).

The herbal drugs, their important chemical constituents and medicinal uses are tabulated. Home remedies for coughs due to colds, allergies and sinus infections are treated with a number of over-the counter medicines. However, for those who prefer to avoid chemicals, the following herbal remedies are recommended to suppress coughs (57).

2.11 Current tools for evaluated cough

The more recent advances and needs in the assessment and measurement of cough, and will not necessarily be comprehensive in its approach. First, I will evaluate the need for determining the inflammatory component particularly the eosinophil count in the evaluation of the cough patient. Secondly, very little has been done so far in assessing the extent and the severity of the cough itself. In this regard, tools such as cough counter, analysis of the cough sound itself, and the impact of the cough on quality of life measures are being developed.

2.11.1 Assessment of airway eosinophilia

A non-invasive method for assessing airway inflammation has been developed over the last 5 years, and this allows one to determine the cellular characteristics of airway inflammation repeatedly with little risk of adverse events to the patient (58).

2.11.2 Assessment and evaluation of cough

The measurement and assessment of cough is important for two reasons: to determine the severity of cough, and to measure the effect of treatments on the severity of cough. This has not been comprehensively examined, in that all the different aspects of the cough assessment have not yet been performed. Evaluation of cough has so far rested mainly on the patient's perception and assessment of the severity of the cough, based on a 5-point scale (59).

2.11.3 Quality of life

Chronic cough can certainly affect quality of life. The author investigated the contribution that chronic cough may have on quality of life of patients with diseases such as cystic fibrosis and bronchiectasis. Patients assessed cough frequency using a diary, and cough impact on their daily living using a specifically devised questionnaire, together with assessment of quality of life using the St George's Respiratory Questionnaire (SGRQ) and the general health questionnaire (SF36). In these patients with moderately severe to severe cystic fibrosis and bronchiectasis, cough impacts, cough frequency, SGRQ and physical components of SF36 were markedly impaired compared with controls. The cough impact and to a lesser extent the cough frequency was a strong determinant of SGRQ quality of life in cystic fibrosis. This indicates that cough itself in these severe diseases has a major impact on quality of life, which is not only due to the number of coughs alone.

Leicester Cough Questionnaire (LCQ) is an English-born self-reporting quality of life measure of acute and chronic cough, developed by S.S. Birring. It consists of 19 items with a 7 point Likert response scale (range from 1 to 7), a format example is available here. Each item is developed to assess symptoms during cough and impact of cough on three main domains: physical, psychological and social. Scores are calculated as a mean of each domain and total score is calculated by adding every domain score (60)

2.12 Systematic review design

2.12.1 Systematic review

Systematic reviews are a type of literature review that uses systematic methods to collect secondary data, critically appraise research studies, and synthesize studies. Systematic reviews formulate research questions that are broad or narrow in scope, and identify and synthesize studies that directly relate to the systematic review question. The designed to provide a complete, exhaustive summary of current evidence relevant to a research question. Systematic reviews of randomized controlled trials are key to the practice of evidence-based medicine, and a review of existing studies is often quicker and cheaper than embarking on a new study (61).

2.12.2 The benefits of a systematic literature review

Systematic review of literature it is important to summarize the knowledge gained from the research. A variety of issues such as research studies in the matter.one may study the same subject. But the different target groups, the operations research, duration of study and measurement tools provide a summary of research on the same subject. Or vary it research needs to be a systematic review of the literature. To analyse and synthesize past research. To search for knowledge is present and used as evidence in a reference work.

Review of knowledge from credible evidence, systematic literature review. Research in the past has been a stepping-stone in the design of research and quality assurance. The research should not exceed 5-10 years. For the modern and present. Compilation of research results to the query are standard and a system to provide a comprehensive study of national and international. And will only select quality work. A valid research process is used to collect research data. And the analysis and synthesis of knowledge.

2.12.3 Data-Analysis and Network meta-analysis

Data-Analysis

Pooled estimate

This step is to assess whether the selected research can be combined. If the study can be combine, it will be the integration process. A study by statistical methods to obtain results the effect sizes of the studies (pooled effect size). There are two methods of pool estimation such as fixed-effect model and random-effects model.

Fixed-effect model was used to test statistics. The research was combined with different not significant statistically. It is a way of determining that the treatment effect is only one and is the only one that all research needs to find out.

Random-effects model was used to test statistics research has brought together a significant difference statistically significant. It cannot be said that the variance is due to any cause. Random effect the hypothesis that the aggregated research is a random sample in the population.

For model selection, either fixed-effect model or Random effects model in analysis if the sum of the study and the confidence of both the model is not very different. It can be concluded that the results are consistent with the selection. Pooled estimate If Heterogeneity is to be found cause and cut off the study that caused the diagnosis. Then combine the results (Pooled estimate) using the same fixed effect model. Heterogeneity There are no differences in education in any aspect. Random effect model. However, analysis with two models yields different results. Depends on style and the results of the study gathered the difference in treatment effect is due to internal variance. And variances between research.

Statistical synthesis and analysis

95% Confidence interval

All 95% confidence intervals will cover the real value of 95 population confidence intervals. If 95% CI stands for null value (1 in the case of ratio), then the hypothesis is tested at $\alpha = 0.05$ using the same statistics to calculate confidence intervals and hypothesis testing found that the p-value> 0.05.

Relative risk

Relative Risk (RR) is the ratio between the incidence of an event (event) used in the case of a comparison of outcome data from two groups to indicate the likelihood of an event with the patient. As a result of the study, compared with the control group, if there is a value of 1, there is no difference between the two groups. If the value is greater than 1 it shows increase the size of the relationship.

Odds ratio

Odds Ratio or handicap is likely to occur in the event of any incident happens and the opportunity to do so.

Heterogeneity.

Q-statistic or Cochrane statistic, with distribution.χ^2test at degree of freedom as k-1 (k = number of trials to be combined), then tested null hypothesis at 0.05.

Percentage of inconsistency index (I^2)

0 - 40% might not be important

30 - 60% may represent moderate heterogeneity

50 - 90% may represent substantial heterogeneity

75 - 100% considerable heterogeneity

Graphically, if researcher find the result in the opposite direction, it is likely to occur heterogeneity.

2.12.4 Herbal medicine for cough within systematic review designs

Herbal medicines are part of a wide range of treatments such as phyto-therapies, hydrotherapies, and Traditional Chinese Medicine (TCM), few of which are applied in conventional medicine. Whilst herbal treatments have a long history of use in varied cultures, randomized controlled trial (RCT) data on their effects is generally lacking.

In since 2009 to 2018 had publication articles around ten studies use SR MA design came to their studies design and included patient with respiratory disease and present cough symptom, 189 came to all studies and intervention had included China traditional herbs and European herbs for remedies cough symptom. For result of all studies showed benefit of use alternative treatment for reduce cough symptom, however all studies report adverse effect from use herbs for mild to moderate symptom included GI symptom, dry eye, rash and other. This method analyses sputum and secretions collected after the patient has inhaled an aerosol of hypertonic saline. Thus, in conditions such as asthma, one expects to see high levels of eosinophil counts, often related to the severity of the disease, in addition to raised levels of neutrophils, which are particularly seen in patients with more severe asthma needing oral corticosteroid therapy.

All study trials were publication in 2009-2018, 4 trials were from china, 5 trials from European and one trial from Korea. Clinical research were included around 189 articles from the word wide

All 10 trials had difference of trial characteristic such as: 4 trials included patient with URTI, 2 trial with chronic cough because duration of present symptom less than 8 week, 2 trial with acute cough, one trial with viral infection and last one don’t definition about cough classify they included. In addition patient were included both adult and children. For tool for assessment for risk of bias their used Cochrane tool.

Table 1 Systematic review and meta-analysis trials characteristic

Number	Author	Year	Country	Topic	Trial include
1	Jiang, H. L	2009	China	Tanreqing Injection for community-acquired pneumonia	12 trial
2	Lopes, L. C	2014	Brazil	Brazilian medicinal plants to treat upper respiratory tract and bronchial illness	Research protocol
3	Luise Wagner	2015	Germany	Herbal Medicine for Cough	9 clinical study
4	Kwan-Il Kim	2015	Korea	A traditional herbal medication, Maekmoondong-tang, for cough	34 clinical study
5	Hongli Jiang	2016	China	Chinese Medicinal Herbs in the Treatment of Upper Airway Cough Syndrome	16 clinical study
6	Song, P	2016	Canada	Clinical Efficacy and Safety of Chinese Herbal Medicine Auxiliary Therapy for Childhood Cough Variant Asthma	20 clinical study
7	Wang, P	2016	China	Tanreqing injection for acute bronchitis disease	49 clinical study
8	Hu, X. Y	2017	UK	Andrographis paniculata (Chuan Xin Lian) for symptomatic relief of acute respiratory tract infections in adults and children	33 clinical study
9	Niu, Q. Q	2017	China	Efficacy and safety of Lianhua Qingwen capsule for influenza	10 clinical study
10	Olabisi Oduwole	2018	Nigeria	Honey for acute cough in children	6 clinical study

Table 2 Trial characteristic of patient, disease and risk of bias tools

Number	Author	Year	Country	Disease	Patient	Risk of bias tools
1	Jiang, H. L	2009	China	Pneumonia	Not report*	Jadad scale
2	Lopes, L. C	2014	Brazil	URTI	Adult and children	Cochrane collaboration risk of bias tool Newcastle-Ottawa
3	Luise Wagner	2015	Germany	Cough	Adult and children	Cochrane Handbook for Systematic Reviews
4	Kwan-Il Kim	2015	Korea	URTI Common cold	Adult and children	Cochrane Back Review Group
5	Hongli Jiang	2016	China	Chronic Cough	Adult and children	Cochrane risk-of-bias system
6	Song, P	2016	Canada	Cough variant asthma Chronic cough	Childhood	Cochrane Hand book
7	Wang, P	2016	China	Acute bronchitis Less than 3 weeks	Adults or children	Cochrane Handbook (Version 5.1.0)
8	Hu, X. Y	2017	UK	ARTIs Less than four weeks	Adults or Children	Cochrane Handbook
9	Niu, Q. Q	2017	China	Influenza	Not report*	Revman5.3 software
10	Olabisi Oduwole	2018	Nigeria	URTI	Children	Cochrane's 'Risk of bias' tool

***not report because hasn't full text**

Table 3 Trial characteristic of methodology in SR MA studies

Number	Author	Year	Country	Inclusion criteria
1	Jiang, H. L	2009	China	Patient with community-acquired pneumonia
2	Lopes, L. C	2014	Brazil	Patient (>18 years old) or pediatric (0–18 years old) Disease: acute cough from upper and lower respiratory disease. Included: common cold, sinusitis, tonsillitis, otitis media, pharyngitis or laryngitis
3	Luise Wagner	2015	Germany	Administered orally to patients with cough were included regardless of age, sex, or underlying disease. Included every variant of MMDT, regardless of the number of herbs added, removed, or replaced in the MMDT archetype.
4	Kwan-Il Kim	2015	Korea	Participants were required to have experienced cough as a symptom of URTI or common cold, in the absence of other chronic disease. There were no limitations on age.
5	Hongli Jiang	2016	China	Patients with UACS (Upper airway cough syndrome)
6	Song, P	2016	Canada	Patients with childhood CVA (Cough variant asthma) Patients between 0-14 years of age, of both sexes TRQ plus antibiotics versus antibiotics.
7	Wang, P	2016	China	TRQ versus antibiotics plus antiviral drugs. TRQ plus conventional therapy versus conventional therapy. Patients diagnosed as AB (acute bronchitis), adults or children, Without limitation in ages, gender.
8	Hu, X. Y	2017	UK	All ages, with symptoms of ARTIs and Diagnoses of upper or lower ARTIs include acute common cold, influenza, rhinosinusitis, laryngitis, tonsillitis, pharyngitis, croup,acute otitismedia bronchitis, pneumonia, and acute exacerbations of COPD.
9	Niu, Q. Q	2017	China	Patient with influenza
10	Olabisi Oduwole	2018	Nigeria	Children aged 12 months to 18 years. Patient with cough caused by acute viral or bacterial URTI.

Table 4 Summary for intervention characteristic of all trial

Number	Author	Year	Country	Intervention
1	Jiang, H. L	2009	China	Tanreqing Injection (compound traditional Chinese herbal medicine)
2	Lopes, L. C	2014	Brazil	15 herb of the Brazilian herbal medicines: Ananas comosus (L.) Merr., Bromeliaceae; Echinacea purpurea (L.) Moench, Asteraceae; Eucalyptus globulus Labill., Myrtaceae; Glycyrrhiza glabra L., Fabaceae; Hedera helix L., Araliaceae; Malva sylvestris L., Malvaceae; Mentha spp, Lamiaceae; Mikania glomerata, Asteraceae; Pelargonium sidoides DC., Geraniaceae; Petasites hybridus (L.) G. Gaertn., B. Mey. & Scherb.,Asteraceae; Pimpinella anisum L., Apiaceae; Polygala senega L., Polygalaceae; Psychotria ipecacuanha (Brot.) Stokes, Rubiaceae; Sambucus nigra L., Adoxaceae.
3	Luise Wagner	2015	Germany	Maekmoondong-Tang (MMDT) were consist: Liriope Tuber, Pinellia Tuber Oryzae Semen, Zizhyphi Fructus, Ginseng Radix Alba, Glycyrrhizae Radix et Rhizoma
4	Kwan-Il Kim	2015	Korea	Pelargonium sidoides Echinacea Andrographis paniculata ivy/primrose/thyme essential oils
5	Hongli Jiang	2016	China	bakumondoto Chinese medicinal herbs (CMH): not report about kind of herbs.

Table 4 (continued)

Number	Author	Year	Country	Intervention
6	Song, P	2016	Canada	Chinese herbal medicine auxiliary therapy (CHMAT)
7	Wang, P	2016	China	Tanreqing injection extracted from five kinds of traditional Chinese medicines (TCM): Radix scutellariae. Forsythia suspense. Flos lonicerae. Bear gall powder. Cornu gorais.
8	Hu, X. Y	2017	UK	A. Paniculata (as a mono-therapy and as a herbal mixture)
9	Niu, Q. Q	2017	China	Japanese Honeysuckle Flower: (*Lonicera japonica*) Ephedra Herb (honey-fried): (*Ephedra sinica*) Bitter Apricot Seed (stir-baked): (*Prunus armeniaca*) Isatis Root: (*Isatis tinctoria*) Male Fern Rhizome, (*Tracheophyta*) Heartleaf Houttuynia Herb: (*Houttuynia cordata* Thunb) Cablin Patchouli Herb: (*Pogostemon cablin*) Rhubarb, Bigflower Rhodiola Root: (*Rhodiola rosea* L) Liquorice Root: (*Glycyrrhiza glabra* L)
10	Olabisi Oduwole	2018	Nigeria	Honey

Table 5 Summary of result and adverse event from all trials

Number	Author	Year	Country	Result	Adverse event
1	Jiang, H. L	2009	China	Meta-analysis showed that compared with oseltamivir, Lianhua Qingwen capsule was more effective in alleviating flu-symptoms included: The time of cough disappeared SMD=-0.39, 95%CI-0.57, -0.21].	Not report
2	Lopes, L. C	2014	Brazil	Research protocol	
3	Luise Wagner	2015	Germany	MMDT reduced the severity of cough by 74% compared with the conventional antitussive medications in various conditions (n=1145; RR of cough persisting	One case of rash was likely to be attributed to MMDT
4	Kwan-Il Kim	2015	Korea	After treatment: 0.26; 95% CI, 0.19–0.34, I^2: 0%). Strong evidence for A. paniculata (SMD = –1.00, 95% CI = –1.85,–0.15; P<0.001) ivy/primrose/thyme (RR = 1.40, 95% CI = 1.23, 1.60; P<0.001) In treating cough moderate evidence for P. sidiodes (RR = 4.60; 95% CI = 2.89,7.31;P<0.001), limited evidence for Echinacea (SMD = –0.68; 95% CI = –1.32, –0.04; P = 0.04). 16 trial included had the poor homogeneity of the studies.	A.paniculata: mild adverse effects, including nausea, emesis, vertigo, skin rash and diarrhea. Essential Oils: high rate of adverse events including skin and mucosal irritation. Echinacea: few mild, mainly gastrointestinal
5	Hongli Jiang	2016	China	Compared with Western medicine (WM) showed (1) A higher TCM recovery rate. (2) Better relief of primary symptoms, including cough and postnasal dripping. (3) A reduction in physical signs. (4) a lower risk of cough relapse	No severe adverse events

Table 5 (continued)

Number	Author	Year	Country	Result	Adverse event
6	Song, P	2016	Canada	CHMAT may have positive effects on CVA, leading to better improvement in disorders of cough and asthma.	Observed in five studies 2 cases had palpitation. 4 cases had tiredness. 2 cases had nasopharyngeal dryness. 13 cases had hoarseness. 35 cases had nausea and vomiting. 26 cases had palpitation. 2 cases had tremor; another. 2 cases had tongue numbness, 1 case had dry eyes. 1 case had abdominal pain. 1 case had restlessness. 1 case had drowsiness. 11 cases had fibrillation.
7	Wang, P	2016	China	Resolution of cough: TRQ plus antiviral drugs versus antiviral drugs (MD: −2.09; 95% CI −3.11, −1.43; P < 0.00001) TRQ plus antibiotics versus antibiotics (MD: −2.65; 95% CI −2.88, −2.42; P < 0.00001) TRQ plus conventional therapy versus conventional therapy alone (MD −1.84; 95% CI −2.85, −0.83; P = 0.0003)	Four trials were report: mild skin rash, infusion reaction, hypersensitiveness nausea

Table 5 (continued)

Number	Author	Year	Country	Result	Adverse event
8	Hu, X. Y	2017	UK	A.Paniculata improved cough (n = 596, standardised mean difference SMD: -0.39, 95% confidence interval CI [-0.67, -0.10]) A.Paniculata (alone or plus usual care) Shortened the duration of cough.	constipation Nausea, Vomiting, diarrhoea unpleasant sensations in the chest intensified headache
9	Niu, Q. Q	2017	China	Lianhua Qingwen capsule was more effective in the time of cough disappeared [SMD=-0.39,95%CI (-0.57, -0.2)]	No full text
10	Olabisi Oduwole	2018	Nigeria	Honey probably reduces cough duration to a greater extent than salbutamol or placebo. Honey probably relieves cough symptoms and improves sleep quality for both children and parents better than no treatment. Honey probably reduces cough frequency better than placebo when given to children for a day. Honey probably reduces cough severity, bothersome cough,	mild reactions (nervousness, insomnia, and hyperactivity), gastrointestinal symptoms (stomachache nausea, diarrhoea, and vomiting), Rash, tachycardia, drowsiness, Somnolence.

Herbal medicines are part of a wide range of treatments such as phytotherapies, hydrotherapies, and Traditional Chinese Medicine (TCM), few of which are applied in conventional medicine. Whilst herbal treatments have a long history of use in varied cultures, randomized controlled trial (RCT) data on their effects is generally lacking (17).

In south of Asia such as THAILAND and LAO PDR had old culture and traditional of used herbs for treatment health disorder. Currently have reports about used herb medicines for treatment and relief among health long time ago to the present. The review form Thai and Lao nation list of essential medicine had herbal medicines around seven mix herbs formulations had thirty herbs from Thai nation list of essential medicine (62) and three herbs has use remedies cough in Lao nation list of essential medicine (63).

Table 6 Summary of herbs for relief cough in Thai and Lao drug list

Number	Name	Scientific name
1	ยูคาลิปตัส	*Eucalyptus globulus* Labill
2	มะขามป้อม	*Phyllanthus emblica* L
3	ชะเอมเทศ	*Glycyrrhiza glabra*
4	สะระแหน่	*Mentha x cordifolia* opiz ex fresen
5	สมอพิเภก	*Terminalia bellirica*
6	มะนาว	*Citrus aurantifolia* (Christm.) Swingle
7	บ๊วย	*Prunus mume*
8	กานพลู	*Syzygium aromaticum*
9	สมอไทย	*Terminalia chebula* Retz.
10	อบเชยญวณ	*Cinnamomum loureiroi*
11	หล่อฮั่งก๊วย	*Siraitia grosvenorii*
12	ผิวส้มจีน	*Citrusx sinensis*
13	ชะเอมไทย	*Albizia myriophylla* Benth
14	ขมิ้นอ้อย	*Curcuma zedoaria*
15	กะเพราแดง	*Ociemum tenuiflorum* L.
16	มะแว้งเครือ	*Solanum trilobatum* L.
17	เทียนขาว	*Cuminum cyminum* L.
18	ผักชีลา	*Anethum graveolens* L.
19	ใบสวาด	*Caesalpinia bonduc*
20	ตานหม่อน	*Vernonia elliptica* DC
21	มะแว้งต้น	*Solanum indicum* L.
22	โกฐจุฬาลัมพา	*Artemisia annua* L.
23	น้ำผึ้ง	*Apis mellifera* L.
24	ดีปลี	*Piper longum*
25	ขิง	*Zingiber officinale*
26	พริกไทยล่อน	*Piper nigrum* L.
27	ว่านน้ำ	*Acorus calamus*
28	พิมเสน	*Pogostemon cablin*
29	เก็กฮวย	*Chrysanthemum morifolium* Ramat.
30	เสนียด	*Justicia adhatoda*

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Materials and methods

This study is a systematic review and meta-analysis, the report followed by Cochrane hand book tool the study PRISMA report guidelines 2009 checklist (Appendix A). Step of searching was shown in PRISMA flowchart 2009 (Appendix B)

3.2 Literature search

The literature on herbal medicine used for cough was searched from their inception to March 2019, via the Cochrane Library, PubMed, Scopus, Embase, CINAHL, Springer, Science direct, ProQuest, and Thailis databases.

A range of free text words and indexed terms relate to, “cough” were search as a generic symptom, not related to specific medical conditions or etiologic, and treat with different complementary and alternative medicine approaches. Other search terms focused on “cough” as a symptom of varied respiratory conditions including: “bronchitis”, “common cold”, “respiratory tract infection”, “upper respiratory tract infection”, “lower respiratory tract infection”, “pneumonia”, “chronic pulmonary diseases”, “chronic obstructive pulmonary disease”, “pulmonary disease”, “respiratory dysfunction”, “flu”, and “influenza”.

For search term of herbs, we used words and terms relate to “herbal medicine”, “natural plant”, name of thirty herbs in table 6 including scientific name, common name, and pure extract (Appendix C).

These terms were combination with different herbs. The search terms were modified to adapt to different databases. We used conjunction keywords in similar key word with OR for the most comprehensive results, used the conjunction AND to combined the keyword in different topic for more specific results. (64)

3.3 Eligibility Criteria

To be eligible for review, studies have to meet the following criteria:

Types of studies: RCTs are eligible, but only if published as full research articles.

Types of participants:

Participants require to have cough from upper or lower respiratory tract infection, with all duration including acute, sub-acute and chronic cough. We excluded patient with cough from chronic disease including lung cancer, tuberculosis, severe pneumonia, known immune deficiency, post-extubating and pulmonary fibrosis. There are no limitations on age.

Types of interventions: Studies require to compare herbal medicine to either a placebo, or standard treatment. Herbal medicine studies of herbal interest were included are not the main intervention will be excluded. No limitations imposed concerning the duration of the application, dosage, and form of the herbal medications.

3.4 Selection of studies and data extraction

Two review authors independently screened abstracts identified during the literature search, reading potentially eligible articles in full to determine the extent to which they met the eligibility criteria. Disagreements will discuss with a third reviewer until consensus reach.

Two reviewers (Ladda Her and Juntip Kanjanasilp) systematically extract data regarding from each study publication year, country, study design, disease/condition, participants(the numbers of enrolments and dropouts, mean age, and cough duration), Herb interventions (composition, dosage, and type of the product), control interventions, concomitant medications, treatment duration, outcome measurements (cough symptom assessment, quality of life), and adverse events. Discrepancies will resolve by discussion between the two reviewers or by consultation with the third arbitration (Ratree Sawangjit).

3.5 Outcome measures

About this study we did in two steps:

First step was included trials review. For second step, meta-analysis was presented if all included trial have measure in the same outcome and can mix together.

The following primary outcome measures were included in this study:

Participant self-report or clinician/observer assessment on overall cough symptoms; common use measures or tools include:

Changes on visual analogue scales (VAS).

Changes in symptoms scored on a Likert-type scale.

Global assessment of symptom improvement by the patient.

Global assessment of symptom improvement by treating clinician.

For secondary outcome measures were included in this study

Adverse events: included any anaphylactic, allergic reactions, hypersensitivity reactions, or complications of herbal medicine use, such as rash, nausea, fatigue, or worsening of respiratory symptoms.

We defined serious AEs according to any event that leads to death, is life-threatening, requires hospitalisation or leads to persistent or significant disability; biochemistry results such as electrolytes, liver and kidney function tests (alanine aminotransferase and creatinine).

3.6 Assessment of risk of bias in included studies

The risk of bias of the included RCTs were assessed independently by two reviewers using Ladda HER and Juntip Kanjanasilp using ROB version 2.0 from the Cochrane Handbook for Systematic Reviews of Interventions tool. We assessed bias over the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of researchers conducting outcome assessments), and attrition bias (incomplete outcome data), and reporting bias (selective reporting), and other sources of bias. A judgement of ‘low risk’ of bias, ‘high risk’ or bias, or ‘some

concern risk' of bias was provide for each domain. Any disagreements will resolve by discussion or by involving a third reviewer until consensus will reach.

3.7 Measures of treatment effect

Data from individual studies were included in our study are combination in a meta-analysis when interventions were performed in a homogeneous clinical outcome, similar population, intervention and comparison.

We used STATA program version 14 and used Meta command for analysis data.

The impact of herbs intervention in continuous variables, such as all cough symptom scores, will express as mean end of study (Mean) with 95% confidence interval (CI).

While its impact on binary variables will express as risk ratio (RR) with 95% CI. For the RR estimate of response rate such as symptoms unchanged or worsened, improvement even after herbal medicine treatment.

3.8 Dealing with missing data

For missing or incomplete data, we contacted to study authors to obtain this where possible. If the means were reported without standard deviations, we will calculate the standard deviation from the information reported such as p-values, confidence intervals. As far as possible, we will utilise intention to treat (ITT) analysis data for all outcomes. However, if all most include trials report complete cases only; and complete case data is the primary analysis dataset. For each outcome, the number of participants whose data available at baseline and at follow up, and the rate of loss to follow-up will record.

3.9 Assessment of heterogeneity

Between-study heterogeneity were assessed by using the I^2- statistic which describes the percentage of variation across studies that is due to heterogeneity rather

than chance. Rules of thumb for interpretation of this statistic suggest that I^2>30% equates to moderate heterogeneity, I^2>50% equates to substantial heterogeneity and I^2>75% equates to considerable heterogeneity. For all I^2 values above 50%, we will investigate potential sources of heterogeneity.

Although this threshold is widely used, it is somewhat arbitrary and therefore if the I^2 value below 50% but the direction and magnitude of treatment effects suggest important heterogeneity, we will use the fix effect model and investigate the potential sources in a sensitivity analysis and took this into account when interpreting the findings.

As high levels of heterogeneity will expect due to complexity in the form of herbs (e.g. monotherapy or herbal combination, capsule or liquid), it will plan to use a random effects model to pool the overall effects and the underlying disease/condition, the use scales, and the herbal compositions of herb intervention will expect to vary a cross the study.

3.10 Subgroup analysis

Subgroup analysis was performed to reduce other factors that may affect the analysis.

- Patients with upper respiratory tract infection versus lower respiratory tract infection.
- Patients with acute cough versus chronic cough.
- Adults versus children (younger than 18).
- Herbs as monotherapy versus as fix combinations.
- Herbs in different preparation, e.g. versus capsule or other forms.
- Herbs versus placebo.
- Herbs versus standard treatment.

The statistics in the analysis of subgroups are the same as the total group analysis.

CHAPTER 4
RESULT

4.1 Description of included trials

The literature searched from 9 electronic databases and using 30 names of herbals in national list of essential medicine of Thai and Lao PDR. The number of studies was identified in 1,745 potentially relevant articles. Time of searching on all databases was started from their inception to March 2019, in our search no limited both in years on public and language, however, trials were included in this study focusing on a research study in humans and used herbs comparing with placebo or standard treatment for reducing cough symptom. All included trials characteristic were showed data in Table 7.

All data was searched by the author for using a search term such as part of symptom, combined with the scientific name of 30 herbs in both Thailand and Lao PDR national list of essential medicine. After the process search finished, we found 1,745 articles to consistent our search terms. However, we found a study with four kinds of herbs including eucalyptus, honey, ginger, and malabar nut. The twenty-six herbs in formula used to reduce cough were not found. After that, all removing duplicates and screening the article titles and abstracts for study design, symptoms, and wrong intervention articles were excluded 1,724 articles. Finally, the author included 20 studies in the systematic review. Finding 6 RCTs (65-70) for eucalyptus (*Eucalyptus globulus Labill*), 10 RCTs (67, 71-79) for honey, 3 RCTs (80-82) for ginger (*Zingiber officinale*), and 2 RCTs (83, 84) for malabar nut (*Justicia adhatoda*). One study (67) reported intervention with mix herbs honey and eucalyptus, when we explained data of this study were separated by focus intervention in each herb. Moreover, one study (69) from eucalyptus was not reported information of cough in the full text and authors of this trial were contacted for further information but we don't have any responded from them. Meta-analysis had included 15 studies following by study outcome. Figure 1 is a flowchart in the form of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

In the part of systematic review, all 21 RCTs were included from ten databases. The included trials were published between 2000 and 2017. Four of included articles originated (Ben-Arye, E.2012, Cohen, H.A.2012, 2016) (67, 68, 77) in Israel and from Germany (Worth, Heinrich 2009, Fischer, J 2013, Gillissen, A 2013, Matthys, H.2000) (65, 66, 69, 70), three articles (Shadkham et al., 2009, Mohammad et al., 2013, Ayazi et al., 2017) (72, 73, 79) from Iran, two articles (Mario and Sopo et al., 2014)(74, 75) from Italy, two articles (Thomas et al., 2007 and Claire et al., 2014) (80, 81) from United kingdom, two articles (Narimanian et al., 2005 and Barth et al., 2015) (83, 84) from Armenia, and one from Kenya (Waris, A 2014) (76), Hershey (Paul et al., 2007) (71), China (Lei Wang et al., 2010)(82) and Brazil (Peixoto et al., 2016) (78), respectively.

The number of population from 20 RCTs were 3,668 participants. Adult's trial from 11 studies age range above 18 years and children from 9 studies age range between 1-14 years. 1,538 were males and 2,040 were females, three studies did not report data of gender. For all trial described about patient's cough symptom caused including acute bronchitis from 3 studies in eucalyptus (*Eucalyptus globulus* Labill) study; upper respiratory infection 12 studies in eucalyptus study (*Eucalyptus globulus Labill*), honey, and jasticia study (*Justicia adhatoda*); chronic obstructive pulmonary and influenza in ginger study (*Zingiber officinale*).

The duration of cough symptom was presented by patient status including time less than one week reported in 13 studies, more than two weeks 3 studies, and 5 studies not reported of symptom time. Duration of follow up in were difference; time less than 2 weeks from 17 studies and more than 2 weeks in 2 studies. All trials had presented time of cough symptom presentation and follow up that showed in **Table 8**.

Figure 1 PRISMA flowchart

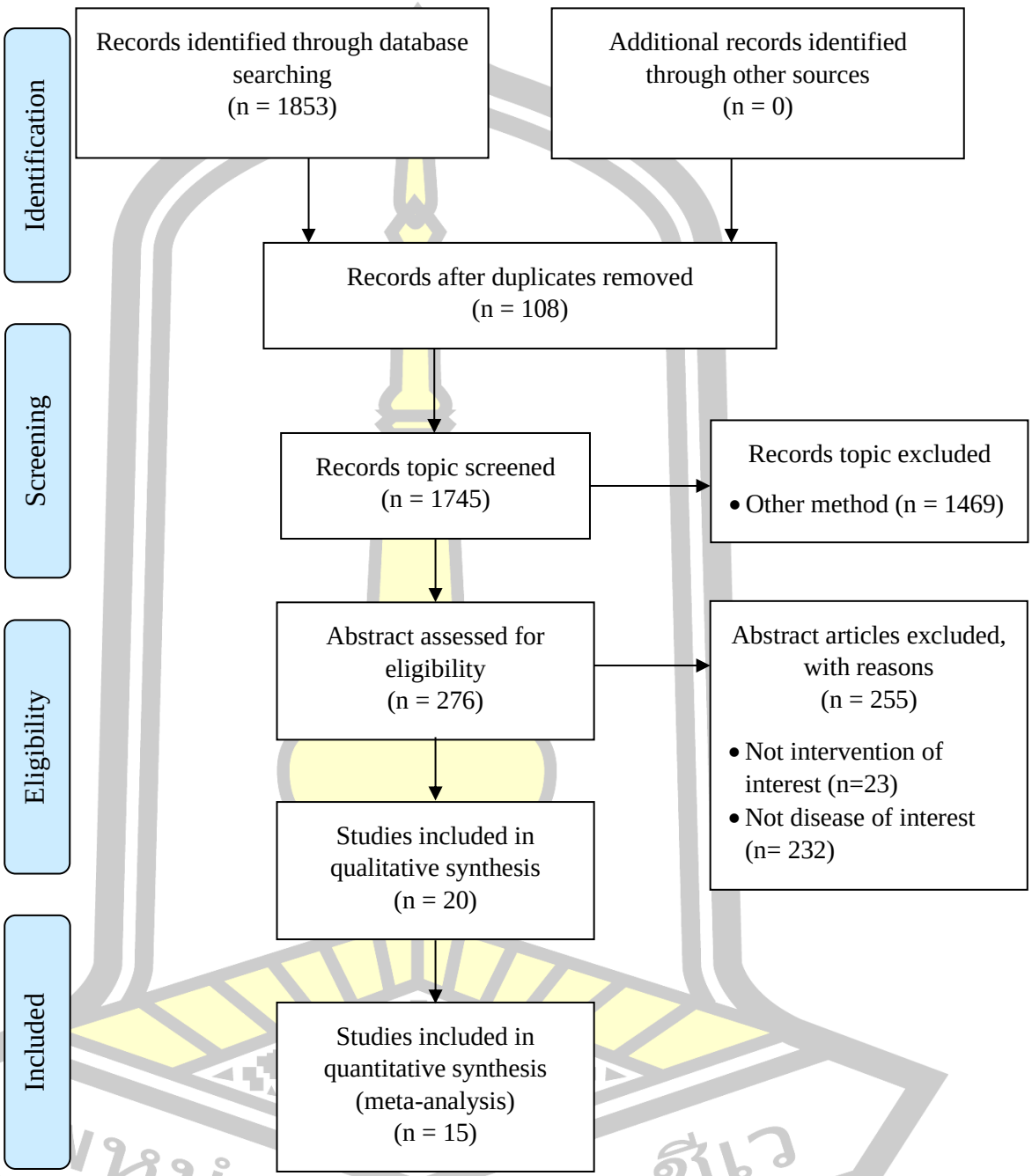


Table 7 all included trials characteristics

No.	Author	Year	Country	Study design	Sample sizes		Age	Sex		Patient
					Intervention	Control		Male	Female	
1	Heinrich	2000	Germany	A multi-center, RCT, double blind, parallel-group.	170	506	>=18	283	393	Adult
2	Narimanian, M.	2005	Armenia	A center, RCT, double blind, Parallel-group.	30	60	18-54	28	62	Adult
3	Michael.	2007	UK	A center, double-blind, placebo-controlled, cross-over study	16	16	18-75	7	25	Adult
4	Paul	2007	Hershey	A center, RCT, single blind, Parallel-group.	35	73	2-18	NI	NI	Pediatric
5	Heinrich	2009	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	110	110	40-80	51	79	Adult
6	Shadkam	2009	Iran	A center, RCT, parallel-group.	33	106	2-5	71	68	Pediatric
7	Eran Ben-Arye	2010	Israel	A multi-center, RCT, double-blind trial, a placebo-controlled	26	34	21-66	32	28	Adult
8	Lei Wang	2010	China	a multi-center, RCT, double-blind, placebo-controlled trial	360	120	18-65	189	278	Adult
9	Herman	2012	Israel	A multi-center, RCT, double-blind trial, a placebo-controlled	75	225	1-5	124	176	Pediatric
10	Juergen	2013	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	121	121	18-70	104	138	Adult
11	Gillissen, A.	2013	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	202	211	>=18	181	217	Adult
12	Mohammad	2013	Iran	A center, RCT, double blind, Parallel-group.	29	56	>=18	51	34	Adult
13	Mario	2014	Italy	A multi-center, RCT, double-blind trial, a placebo-controlled	51	51	3-6	54	48	Pediatric
14	Miceli Sopo	2014	Italy	A multi-center, RCT , double-blind Open-label; no placebo group	71	63	2-14	NI	NI	Pediatric
15	Waris, A.	2014	Kenya	A center, RCT, double blind, Parallel-group.	57	88	1-12	70	67	Pediatric
16	Claire	2014	UK	A center, RCT, double-blind, placebo-controlled, parallel-group	20	13	>18	19	14	Adult
17	Anders	2015	Armenia	A comparative, RCT, double-blind, placebo-controlled study	66	111	18-65	76	101	Adult
18	Herman	2016	Israel	Multi-centre, RCT, single-blinded, parallel-group	78	72	2-5	71	79	Pediatric
19	Peixoto	2016	Brazil	A center, RCT, double-blind, placebo-controlled, parallel-group	29	31	2-15	26	34	Pediatric
20	Parviz	2017	Iran	A center, RCT, not-blind, placebo-controlled, parallel-group	71	21	1-12	NI	NI	Pediatric

Table 8 all included trial characteristics of symptom presentation and follow up

No.	Author	Year	Country	Study design	Age	Patient	Disease	Symptom (Days)	Follow up (Days)
1	Matthys	2000	Germany	A multi-center, RCT, double blind, parallel-group.	>=18	Adult	Acute bronchitis induce cough	> 5	28
2	Narimanian	2005	Armenia	A center, RCT, double blind, Parallel-group.	18-54	Adult	URI induce cough	NI	8
3	Thomas	2007	UK	A center, double-blind, placebo-controlled, cross-over study	18-75	Adult	Asthma induce cough	NI	252
4	Paul	2007	Hershey	A center, RCT, single blind, Parallel-group.	2-18	Pediatric	URI induce cough	< 7	2
5	Worth	2009	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	40-80	Adult	COPD	> 3	180
6	Shadkam	2009	Iran	A center, RCT, parallel-group.	2-5	Pediatric	URI induce cough	> 5	1
7	Ben-Arye	2010	Israel	A multi-center, RCT, double-blind trial, a placebo-controlled	21-66	Adult	URI induce cough	NI	3
8	Wang	2010	China	A multi-center, RCT, double-blind, placebo-controlled trial	18-65	Adult	Influenza induce cough	> 1	3
9	Cochen	2012	Israel	A multi-center, RCT, double-blind trial, a placebo-controlled	1-5	Pediatric	URI induce cough	< 7	3
10	Fischer	2013	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	18-70	Adult	Acute bronchitis induce cough	> 7	10
11	Gillissen	2013	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	>=18	Adult	Acute bronchitis induce cough	2	14
12	Ali Raeessi	2013	Iran	A center, RCT, double blind, Parallel-group.	>=18	Adult	Presisting cough	> 21	7
13	Canciani	2014	Italy	A multi-center, RCT, double-blind trial, a placebo-controlled	3-6	Pediatric	Presisting cough	7-21	8
14	Miceli Sopo	2014	Italy	A multi-center, RCT , double-blind Open-label; no placebo group	2-14	Pediatric	URI induce cough	> 7	3
15	Waris	2014	Kenya	A center, RCT, double blind, Parallel-group.	1-12	Pediatric	URI induce cough	NI	5
16	Brockwell	2014	UK	A center, RCT, double-blind, placebo-controlled, parallel-group	>18	Adult	COPD presistent cough	NI	7
17	Barth	2015	Armenia	A comparative, RCT, double-blind, placebo-controlled study	18-65	Adult	URI induce cough	< 1	5
18	Avner Cohen	2016	Israel	A multi-centre, RCT, single-blinded, parallel-group	2-5	Pediatric	URI induce cough	> 7	3
19	Peixoto	2016	Brazil	A center, RCT, double-blind, placebo-controlled, parallel-group	2-15	Pediatric	URI induce cough	1	1
20	Ayazi	2017	Iran	A center, RCT, not-blind, placebo-controlled, parallel-group	1-12	Pediatric	URI induce cough	>7	2

4.2 Risk of Bias in Individual Studies.

Two review authors independently assessed the methodological quality of all included studies according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions. Data risk of bias reported in **Figure 2 and 3.**

No.	Author	Year	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
1	Matthys, H.	2000	+	+	+	+	+	+
2	Worth, Heinrich	2009	+	+	-	+	-	-
3	Ben-Arye, E.	2010	+	+	+	+	+	+
4	Cohen, H. A.	2012	+	+	-	+	+	-
5	Fischer, J.	2013	+	+	+	+	+	+
6	Gillissen, A.	2013	+	+	-	+	+	-
7	Ian M. Paul	2007	+	-	-	+	+	-
8	Shadkam, M. N.	2009	+	?	+	+	+	?
9	Raeessi, M. A.	2013	+	+	-	+	+	-
10	Canciani, M.	2014	+	+	+	+	+	+
11	Sopo, S. M.	2014	+	+	+	+	+	+
12	Waris, A.	2014	+	+	+	+	+	+
13	Cohen, H. A.	2016	+	+	+	+	+	+
14	Peixoto	2016	+	+	+	+	+	+
15	Ayazi, P.	2017	?	-	-	+	+	-
16	Thomas, M.	2007	+	+	?	+	+	-
17	Wang, Lei	2010	+	+	+	+	+	+
18	Brockwell, C.	2014	+	+	+	+	+	+
19	Narimanian, M.	2005	+	+	+	+	+	+
20	Barth, A.	2015	+	+	+	+	+	+

Figure 2 Risk of bias¨ summary review authors' judgements

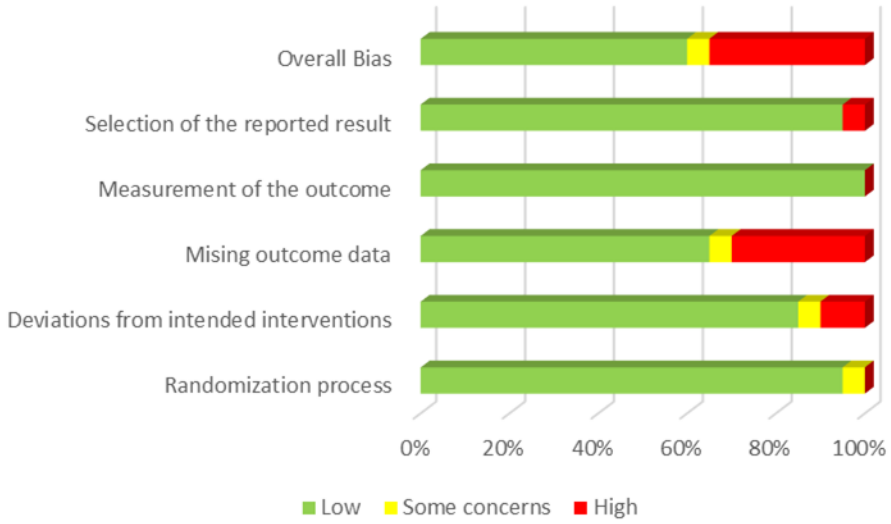


Figure 3 Risk of bias graph

4.2.1 Allocation of studies included

We rated all twenty included studies and were assessed nineteen studies (64-77, 79-83) as low risk (95 percentage) for allocation concealment bias and we rated a study (78) as at some concern of bias (5 percentage) for this domain. Because study 2017 not elucidate the process of random allocation.

4.2.2 Blinding of studies included

We rated seventeen studies (64-70, 72-77, 79-83) as low risk (85 percentage) for performance and detection bias. We assessed two studies at a high risk of bias (10 percentage) for this domain (70, 78). Because the study 2017 (Ayazi, P et al, 2017) was not explained for their process of blinding parents about the treatment type, the presenter revealed the identity of the treatment. The study was not blinded due to the appearance. And next study 2007 as at high risk of bias, because all outcomes were subjective: participants knowing they received no treatment could have influenced performance and assessment of the outcomes. We assessed one study as at some concern risk of bias (5 percentage) for this domain (71) because of this study no information about blinding patients or researchers.

4.2.3 Incomplete outcome data of included trials

We assessed thirteen studies as low risk of bias (65 percentage) of attrition bias (65, 67, 69, 71, 73-77, 79, 82, 83). We assessed one study 2007 (Ian M. Paul et al, 2007) as at some concern (5 percentage) of attrition bias (80). They not explained about a number of patient dropouts and on calculate step they were used number patient of end of the study. We assessed six studies (64, 66, 68, 70, 72, 78) as at high risk of bias (30 percentage) of attrition bias, attrition unclear if reasons for attrition was related to the studies reported. That patients were either lost to follow-up or withdrawn for violating the protocol and other that number of patient drop out more than 10 percentage (64, 66, 72) were not calculated in end of the study.

For measurement of the outcome found in all studies had a low risk of bias because the author not used both multiple tools assessment in one outcome and statistic test to calculated their data

4.2.4 Selective reporting

We rated nineteen studies as low risk of bias for selective reporting; all outcomes proposed in the methods sections were reported in results. Another that, we found as high risk of bias of attrition bias in one study (68). Because this study not reported data of cough. Finally, most result better of methodology and limited in some studies with missing outcome data.

4.2.5 Overall risk of bias from study inclusion

We rated overall risk of bias for twelve studies as low risk (65, 67, 69, 73-77, 79, 81-83), one study as some concerns risk (71), seven studies as high risk (64, 66, 68, 70, 72, 78, 80).

4.3 Descriptions of herbs trials inclusion

4.3.1 Eucalyptus (*Eucalyptus globulus* Labill)

4.3.1.1 Eucalyptus trial characteristics

We searched 340 studies. Screening title and abstract, the 6 trials (65-70) were included in our studies. We included the 5 trials to meta-analysis. All six trials were published since 2000-2013. The 4 trials located in Germany (65, 66, 69, 70) and two trials in Israel (67, 68). Data of eucalyptus trials were presented in table 7.

The five trials reported comparison with placebo, active control, and standard treatment. The number of populations from 6 RCTs were 1,911 participants. Adult's trial from 5 studies (age above 18 years) and children from 1 studies, age between 1-5 years old. Eight hundred and sixty five males and 1,031 females.

The 3 RCTs included patient with acute bronchitis induce cough (65, 66, 70), 2 RCTs in upper respiratory tract infection induce cough symptom (67, 68) and one RCTs with COPD (69), which the duration of symptom presentation less than 1 week reported in four studies (65, 67, 69, 70), and more than one week in one study (66).

Overall data of six trials were reported differences form as a mono-herb and as a mixture with other herbs such as four trials (65, 67, 68, 70) with a mixture between eucalyptus extract, or cineole, mixture with other herbs. Two trials (66, 69) were reported with eucalyptus pure extract. Table 9 presents the characteristics of the study of *Eucalyptus globulus* Labill. The four trials used eucalyptus in capsule (65, 66, 69, 70), one trial used in the spray (68) and the other one used in syrup (67).

Four trials were reported eucalyptus dosage regimen as the capsule form and given dose 100 mg (Heinrich et al., 2009) (69), 200 mg (Juergen et al., 2013) (66) , 300 mg (Heinrich et al., 2000, Gillissen, 2013) (65, 70), spray 40 mcg then 60 mcg (Eran Ben-Arye et al., 2010) (68), and syrup 10 g (Herman et al., 2012) (67). One trial recommends once daily for one day, 4 trials recommended three-time daily (TID) and four-time daily (QID) and the last trial recommends 5 times a day.

Two trials compare eucalyptus with active control (67, 68) included citrus honey; labiatae honey, silan date extract, and polysorbate; lemon, while in the 3 trials (65, 66, 69) did not told the details of placebo. In addition, one trial compares

with active intervention such as cefuroxime and ambroxol. All the 6 trials explained of the preparation study medication in similarly included doses, dosage regimen, and medication form.

4.3.1.2 Outcome measurements of Eucalyptus trial

The most commonly reported primary outcome measure was used subjective evaluation, methods assessed the clinical efficacy of the administered herbal cough remedies. Data of this domain was shown in Table 10.

The methods of outcome measures included symptom diaries, total daily symptom scores and symptom-related questionnaires completed by patients. Common assessment instruments, such as verbal rating scales, 5 items questionnaire was also used to facilitate comparison of the resulting study data changes in patients' symptoms. All the 6 trials assessed cough symptom improvement, the 4 trials (65-67, 69) assessed the cough frequency, 2 studies (65, 67) assessed the cough severity, and quality of patient sleep, 3 studies reported (67, 68, 70) of summary scores of cough symptom, and quality of children sleep and bothersome cough were reported in one study (67). Then, 5 trials reported secondary outcome included adverse events of both group comparison.

For all the 6 trials used tools of assessment cough symptom. Two trials used verbal rating scale (VRS) and this tool had 5 points "very good; good, moderate, bad, very bad" and 7-point Likert scale "scores 0 = no coughing fits per day, 1 = one coughing fit per day, 2 = 2 - 3 coughing fits per day (i.e. occasionally), 3 = 4 – 5 coughing fits per day, 4 = 4 – 9 coughing fits per day (i.e. Frequent), 5 = > 15 coughing fits per day", the 2 trials used one question with 6 point Likert scale "scores: 0 = never, 1 = rarely, 2 = occasionally, 3 = often, 4 = very often, 5 = nearly continuously" and 4 points scale "0: no symptoms, 1: mild, 2: moderate, and 3: severe".

Five studies were included in meta-analysis. Three trials measured cough frequency and reported in mean ± SD. Mix scores of cough had been reported from 2 trials in number of patient's response.

Table 9 Eucalyptus trials' intervention and control group characteristic

No.	Author	Year	Country	Patient	Intervention	Medication form	Control
1	Matthys	2000	Germany	Adult	Myrtol® 300 mg(Mixture)	Capsule	Cefuroxime; ambroxol; placebo
2	Worth	2009	Germany	Adult	Eucalyptol 100 mg (Mono herb)	Capsule	Placebo (No information of formula)
3	Ben-Arye	2010	Israel	Adult	Aromatic herbs 60 mcg (Mixture)	Spray	Placebo: water; polysorbate; lemon.
4	Cohen	2012	Israel	Pediatric	Eucalyptus honey 10 g (Mixture)	Syrup	Citrus honey; labiatae honey, silan date extract
5	Fischer	2013	Germany	Adult	Cineole 200 mg (Mono herb)	Capsule	Placebo (No information of formula)
6	Gillissen	2013	Germany	Adult	Gelomyrtol® 300 mg (Mixture)	Capsule	Placebo (No information of formula)

Table 10 Eucalyptus trials' intervention characteristic

No.	Author	Year	Country	Patient	Intervention	Medication form	Formula
1	Matthys	2000	Germany	Adult	Myrtol® 300 mg(Mixture)	Capsule	Essential oil derived from Pinus spp (pine), Citrus aurantifolia (lime) Eucalyptus globulus.
2	Worth	2009	Germany	Adult	Eucalyptol 100 mg (Mono herb)	Capsule	Cineole extract from eucalyptus
3	Ben-Arye	2010	Israel	Adult	Aromatic herbs 60 mcg (Mixture)	Spray	20% Mentha piperita, 10% Eucalyptus citriodora, 20% Eucalyptus globulus, 20% Rosmarinus officinalis 30% Origanum syriacum.
4	Cohen	2012	Israel	Pediatric	Eucalyptus honey 10 g (Mixture)	Syrup	Eucalyptus oil and honey
5	Fischer	2013	Germany	Adult	Cineole 200 mg (Mono herb)	Capsule	Cineole 200 mg eucalyptus oil
6	Gillissen	2013	Germany	Adult	Gelomyrtol® 300 mg (Mixture)	Capsule	Essential oil derived from Pinus spp (pine), Citrus aurantifolia (lime) Eucalyptus globulus.

Table 11 Eucalyptus characteristic of outcome measurement

No.	Author	Year	Country	Patient	Intervention	Form	Outcome	Type of data
1	Matthys	2000	Germany	Adult	Myrtol 300 mg(Mixture)	Capsule	MS	Response rate
2	Worth	2009	Germany	Adult	Eucalyptol 100 mg (Mono herb)	Capsule	CF	Not report
3	Ben-Arye	2010	Israel	Adult	Aromatic herbs 60 mcg (Mixture)	Spray	MS	Response rate
4	Cohen	2012	Israel	Pediatric	Eucalyptus honey 10 g (Mixture)	Syrup	CF, CS, SQC, SQP, MS	Means ± SD
5	Fischer	2013	Germany	Adult	Cineole 200 mg (Mono herb)	Capsule	CF	Means ± SD
6	Gillissen	2013	Germany	Adult	Gelomyrtol 300 mg (Mixture)	Capsule	MS, CF, CS,	Means ± SD

MS: Mix scores of cough.

CF: Cough frequency.

CS: Cough severity.

SQC: Sleeping quality children.

SQP: Sleeping quality parent.

SD: standard deviation

4.3.1.3 Effect of eucalyptus intervention for relieve cough symptom

Overall of data from five studies, we explained data analysis, because original data from all studies were shown difference information. Two studies reported in binary outcomes (68, 70), while three studies reported in continuous outcomes (65-67). Subgroup analyses were performed for comparing with placebo and active intervention. Subgroup analysis in other comparison groups of the disease and adults versus children were not performed due to insufficient data. Two studies (68, 70)reported both binary and continuous outcomes.

Two studies compared the reducing overall cough symptom. The statistic shown significant effect in favour of eucalyptus versus placebo group in mix scores of cough symptom (n = 402, RR: 1.40, 95%CI [1.19, 1.65], P-value< 0.0001), with low heterogeneity in these results (I^2 = 1.2%; χ^2 = 1.01; P = 0.314). In case, we evaluated by subgroup analysis in standard treatment and the data show no statistically significant difference between eucalyptus and placebo control (n = 504, RR: 1.20, 95%CI [0.93, 1.12], P-value= 0.688). Data analysis is showed in **Figure 4.**

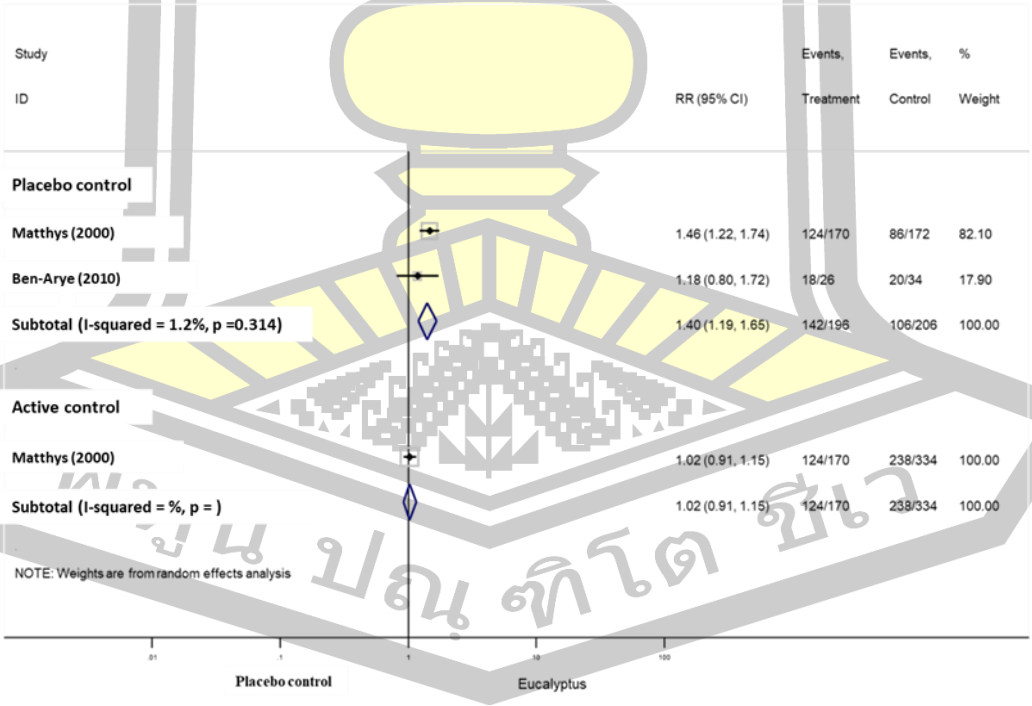


Figure 4. Effects of eucalyptus on mix cough symptom scores

Three RCTs (65-67) reported data in mean ± SD of cough frequency compared between eucalyptus and placebo or active control. Effect of eucalyptus reduced cough frequency not significantly (P = 0.57) and although significant heterogeneity was found in the original study results (n = 955, SMD: -0.22, 95%CI [-1.00 to 0.5], I^2 =93.4%, P<0.0001). Cough severity reduce not statistical significant by eucalyptus (P = 0.23) and although significant heterogeneity was found in the original study results (n = 713, SMD: -1.51, 95%CI [-4.00 to 0.97], I^2 =88.1%, P<0.0001) and overall effect of eucalyptus in both cough frequency and severity did not reduced significantly (P = 0.12) and although significant heterogeneity was found in the original study results (n = 1,668, SMD: -0.54, 95%CI [-1.24 to 0.16], I^2 =91.3%, P<0.0001). Although, on cough frequency outcome data showed no difference between eucalyptus and placebo in reducing cough symptom caused from number of study included when analysis together data no difference in two group. Effects of eucalyptus on cough frequency and severity are shown in **Figure 5.**

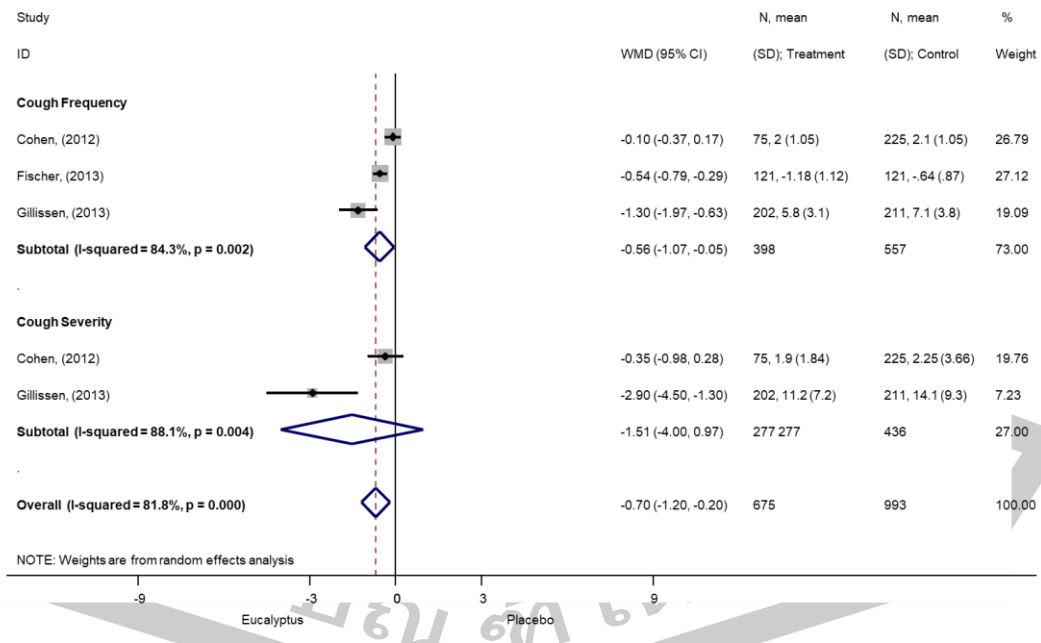


Figure 5 Effects of eucalyptus on cough frequency and severity

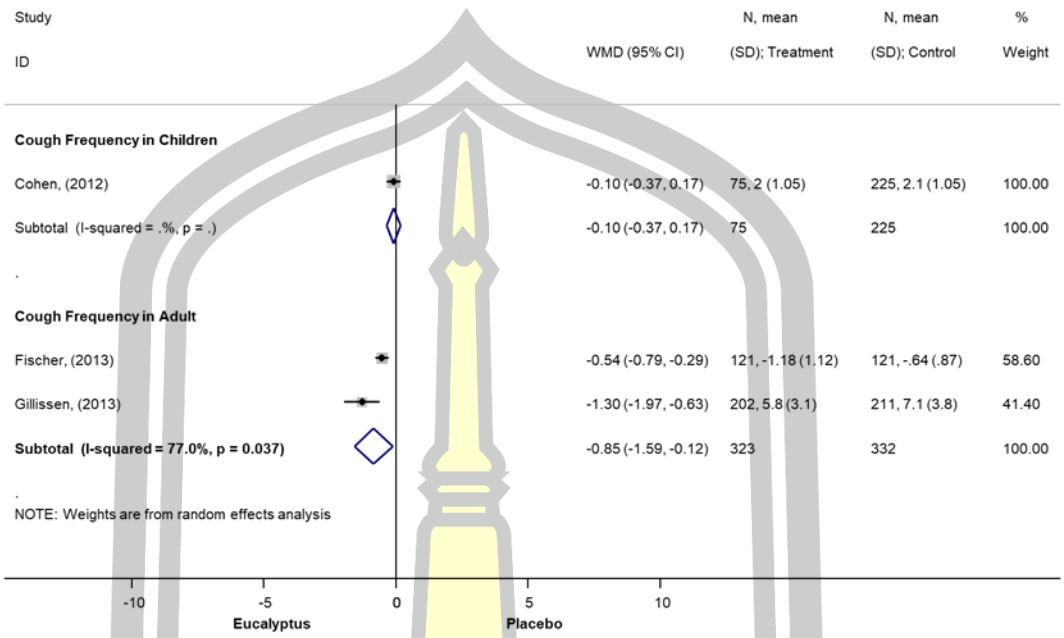


Figure 6 Effects of eucalyptus on cough frequency

4.3.1.4 Adverse event from eucalyptus intervention

Eran Ben (2010)(68) not reported adverse events after received experimental intervention. Because the author explained limitation to concern with the theme of herbal safety. Although they did not observe any severe side effect symptoms, larger-scale studies are warranted to conclude the safety of the aromatic herbal formula. For assessment and following of safety presented data in Heinrich (2000) (70) including evaluated adverse events, vital function (blood pressure and pulse rate), and laboratory screens. Safety data are shown in **Table 12.**

Although, four studies did not present about their criteria of following the safety in experimental intervention, placebo, and active control. But in the result of five studies reported adverse events such as one study (Matthys, H. 2000) (70) reported one serious AE (mild increase in serum hepatic enzymes requiring hospitalization for clarification) in a patient treated with placebo group, 48 AE as of moderate intensity such as 12 AEs in study medication and 36 AEs in placebo and active control group. There were also reported with 83 cases as of mild intensity but the author did not explain about definition of these. In Worth, Heinrich study 2009

(69) reported 9 cases of adverse events from experimental with the cineole group whereas 6 adverse events in the placebo group. Other symptoms in the 3 patients who had nausea, diarrhea, and heartburn were estimated being related to the study medication. Study 2012 (Cohen, H. A.2012) (67) reported adverse events with GI symptom by the parents one case in eucalyptus group. Also, study 2013 reported an adverse event with the same symptom as study 2012 such as gastrointestinal infection in the placebo group. Another that, the cases were reported 3 adverse events in the placebo group included otitis and sinusitis, eye burning, headache, one case, a patient complained of stomach-aches, which was interpreted as being related to the study experimental intervention. Next study, (Gillissen, A.2013) (65) patients had 39 AEs reported such as 21 AEs in the intervention group and 18 AEs in patients of the placebo group. Most of these adverse drug reactions (ADR) were mild-to-moderate intensity including eructation, nausea or mild diarrhea in the study medication and moderate abdominal pain in the placebo group.

Five trials (65-67, 69, 70) reported adverse events and all symptom are GI side effects included nausea, vomiting, diarrhoea, stomach-ache, gastrointestinal infection, and abdominal pain. Meta-analysis from most studies showed safety not statistic significantly different between experimental medication and placebo (n = 1175, RR: 1.02, 95%CI [0.33, 3.14], P-value= 0.971), with a few heterogeneity in these results (I^2 = 36.9%; P = 0.191). Data analysis are shown in **Figure 7.**

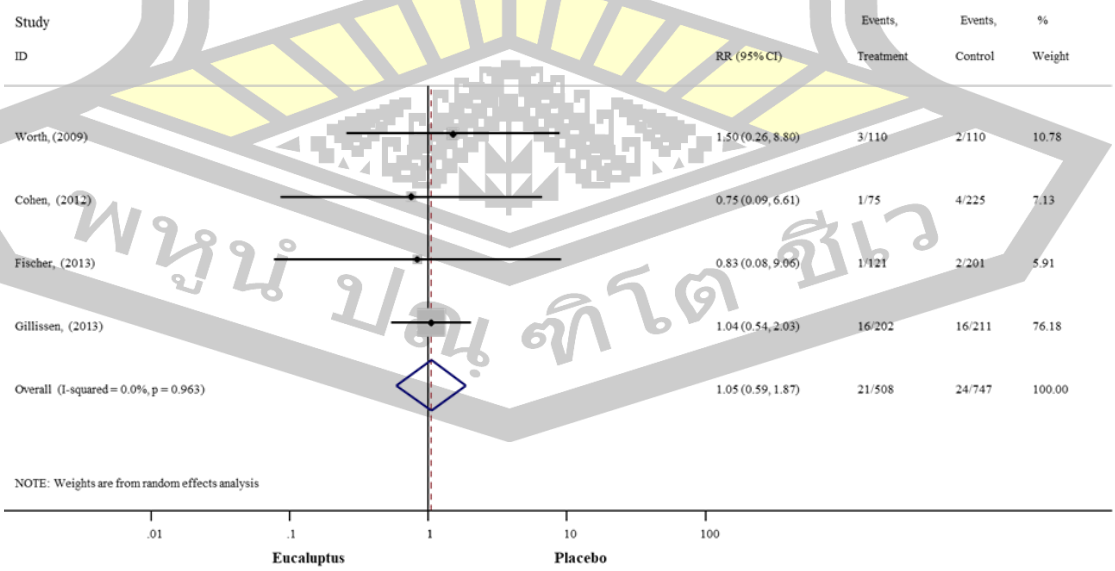


Figure 7 Safety report GI side effect of eucalyptus included trials

Table 12 Eucalyptus trial characteristics of AEs

No.	Author	Year	Country	Study design	Age	Patient	Intervention	Placebo	Adverse event
1	Matthys, H.	2000	Germany	Multi centre, RCT, parallel-group fashion.	>=18	Adult	12	37	Increase hepatic enzymes Moderate intensity
2	Worth, Heinrich	2009	Germany	RCT	40-80	Adult	3	6	Nausea, diarrhoea, heartburn
3	Ben-Arye, E.	2010	Israel	RCT	21-66	Adult	0	0	No information report
4	Cohen, H. A.	2012	Israel	RCT	1-5	Pediatric	1	4	Stomach-ache, nausea, vomiting
5	Fischer, J.	2013	Germany	RCT, parallel-group	18-70	Adult	1	5	Gastrointestinal infection , Otitis, sinusitis, eye burning, headache Stomach-ache
6	Gillissen, A.	2013	Germany	A Multi-centre, RCT	>=18	Adult	13	4	Premature discontinuation Nausea, mild diarrhea Abdominal pain

4.3.2 Honey

4.3.2.1 Honey included trial characteristics

At the literature search yielded 410 articles, a further 400 were excluded after the screening. The end, 10 studies (67, 71-79) remained for the qualitative review and included in the meta-analysis. For ten trials were reported of trials characteristic, all studies were publication year between 2007-2017, with 3 trials from Iran (72, 73, 79), two trials from Italy (74, 75), Israel (67, 77), and the last there studies from Kenya (76), Hershey (71), and Brazil (78). All data were shown characteristic in **Table 13**.

Most of trials designed with randomize control placebo control trial and multi-center. Patients in nine trials included children, age ranges 1-12 years old (9 studies) and one study was adult (age more than 18 years old). The number of participants was included 1,230 children and 85 adults, 489 are males and 574 are the females, the three trials did not tell information about the patient's gender. Patients suffering from upper respiratory tract infection induce cough symptom (8 RCTs) and patients with persisting cough (2 RCTs), which duration of symptom presentation more than 1 week were reported by five studies, between one to three weeks by two studies, and the last one did not tell the information of cough.

For all trial were excluded patients with the diseases such as asthma, pneumonia, laryngotracheobronchitis, sinusitis, allergic rhinitis, chronic lung disease, chronic cardiac or pulmonary condition, malignancy, diabetes, history with herbs allergy, frequent hospitalization, and those who had consumed a drug and herbal that had an effect on sleeping, such as sedatives. There are 8 trials that had difference duration of time follow up, such as less than one week in the 6 studies and the 2 studies reported duration of cough more than one to three weeks. The data are shown in **Table 14.**

Table 13 Honey included trial characteristics

No.	Author	Year	Country	Study design	Sample sizes		Age	Sex		Patient
					Intervention	Control		Male	Female	
1	Paul	2007	Hershey	A center, RCT, single blind, Parallel-group.	35	73	2-18	NI	NI	Pediatric
2	Shadkam	2009	Iran	A center, RCT, parallel-group.	33	106	2-5	71	68	Pediatric
3	Herman	2012	Israel	A multi-center, RCT, double-blind trial, a placebo-controlled	75	225	1-5	124	176	Pediatric
4	Juergen	2013	Germany	A multi-center, RCT, double-blind trial, a placebo-controlled	121	121	18-70	104	138	Adult
5	Mario	2014	Italy	A multi-center, RCT, double-blind trial, a placebo-controlled	51	51	3-6	54	48	Pediatric
6	Miceli Sopo	2014	Italy	A multi-center, RCT , double-blind Open-label; no placebo group	71	63	2-14	NI	NI	Pediatric
7	Waris, A.	2014	Kenya	A center, RCT, double blind, Parallel-group.	57	88	1-12	70	67	Pediatric
8	Herman	2016	Israel	Multi-centre, RCT, single-blinded, parallel-group	78	72	2-5	71	79	Pediatric
9	Peixoto	2016	Brazil	A center, RCT, double-blind, placebo-controlled, parallel-group	29	31	2-15	26	34	Pediatric
10	Parviz	2017	Iran	A center, RCT, not-blind, placebo-controlled, parallel-group	71	21	1-12	NI	NI	Pediatric

Table 14 Honey included trials characteristics

No.	Author	Year	Country	Study design	Age	Patient	Disease	Symptom (Days)	Follow up (Days)
1	Paul	2007	Hershey	A center, RCT, single blind, Parallel-group.	2-18	Pediatric	URI induce cough	< 7	2
2	Shadkam	2009	Iran	A center, RCT, parallel-group.	2-5	Pediatric	URI induce cough	> 5	1
3	Herman	2012	Israel	A multi-center, RCT, double-blind trial, a placebo-controlled	1-5	Pediatric	URI induce cough	< 7	3
4	Mohammad	2013	Iran	A center, RCT, double blind, Parallel-group.	>=18	Adult	Presisting cough	> 21	7
5	Mario	2014	Italy	A multi-center, RCT, double-blind trial, a placebo-controlled	3-6	Pediatric	Presisting cough	7-21	8
6	Miceli Sopo	2014	Italy	A multi-center, RCT , double-blind Open-label; no placebo group	2-14	Pediatric	URI induce cough	> 7	3
7	Waris, A.	2014	Kenya	A center, RCT, double blind, Parallel-group.	1-12	Pediatric	URI induce cough	NI	5
8	Herman	2016	Israel	A multi-centre, RCT, single-blinded, parallel-group	2-5	Pediatric	URI induce cough	> 7	3
9	Peixoto	2016	Brazil	A center, RCT, double-blind, placebo-controlled, parallel-group	2-15	Pediatric	URI induce cough	1	1
10	Parviz	2017	Iran	A center, RCT, not-blind, placebo-controlled, parallel-group	1-12	Pediatric	URI induce cough	>7	2

4.3.2.2 Honey trial characteristic of interventions

Experimental interventions included honey as a monotherapy and as an herbal mixture with other herbs. In **Table 15** is presented the characteristics of honey reported in the included trials. The included trials explained about honey intervention and compared with other herbs or standard treatment.

Difference kind of honey are used included in a trial (72) explained the experimental of natural honey from Kafi-Abad (a village in Yazd) is the capital of Yazd Province, southeast in Iran and study 2007 used as a pure buckwheat honey.

Honey mixture with other herbs such as eucalyptus, citrus, labiatae, and all products were prepared by the Zerifin Breeding Apiary of the Volcari Agricultural Research center in Rechovot, Israel, (67). From the region of the Zagros Mountains in the west of Iran, (73) the polysaccharide-resin-honey product was reported formula by two studies. Canciani, M. (2014) and Cohen, H (2012). Told their formula of the intervention using in their trial, a syrup containing specific fractions of substances such as resins, polysaccharides, saponins, flavonoids and sugars derived from Grindelia robusta, Plantago lanceolata, Helichrysum italicum, honey). This product was supplied by Aboca S.p.A. Società Agricola, Italy. One study reported about their experimental with two kinds of Iranian honeys such as Kimia honey (No. 4916, Kimia, Ardabil, Iran), and Shahde-Golha honey (No. 73294, Shahde-Golha, Khorasan Razavi, Iran). Ardabil and Khora-san Razavi located in Northwest and Northeast of Iran. Two studies reported kind of honey and formula of intervention they are used.

In addition, all trials used honey in difference allocation and the effect of honey compared in difference control group. They reported about the comparison with placebo or standard treatment such as six studies reported intervention of honey compared with placebo. Other studies, the author explained a placebo's formula such as Canciani, M. (2014) that have the placebo contained xanthan gum, citric acid, sugarcane, sorbate potassium (E202), acesulfame K, lemon and orange flavours, plant charcoal and beta-carotene. And a study (Waris, A.2014) told about placebo formula from brown sugar and alcohol free. For Cohen, H. A.(2012), and Peixoto (2016) reported placebo as silan date extract was described, and bromelin and told formula with honey and Ananas comosus extract HBS19820501 (rich in bromelin) as syrup

formulation. However, no information about formula in silant extract. And two studies reported the supportive treatment or no treatment in placebo group.

In case, the intervention compared with active control or standard treatment was reported in the six studies such as dextromethorphan compared with experimental of honey in two studies (Shadkam, M. N.2009 and Sopo, S. M.2014), diphenhydramine was reported in two studies (Shadkam, M. N.2009 and Ayazi, P.2017), honey intervention compared to carbocysteine in Cohen, H. A.2016, levodropropizine in Sopo, S. M.2014, prednisolone and guaifenesin in study of Raeessi, M. A. 2013, and salbutamol in study of Waris, A.2014. The supportive treatment in control group included saline nose drop, water vapour, cleaning a blocked nose, acetaminophen if fever existed were explained by Shadkam, M. N.(2009). About the dosage regimens are shown in **Table 16, 17**.

Table 15 Honey trial characteristics of intervention

No.	Author	Year	Country	Patient	Symptom	Intervention	Form	Dose/day	Dosage regimen
1	Paul	2007	Hershey	Pediatric	URI induce cough*	Honey	Syrup	10 mL	OD
2	Shadkam	2009	Iran	Pediatric	URI induce cough*	Honey	Syrup	2.5 mL	OD
3	Herman	2012	Israel	Pediatric	URI induce cough*	Honey	Syrup	10 mL	OD
4	Juergen	2013	Germany	Adult	Persisting cough	Honey	Jam-like paste	75 mL	TID
5	Mario	2014	Italy	Pediatric	Persisting cough	Grintuss	Syrup	20 mL	QID
6	Miceli Sopo	2014	Italy	Pediatric	URI induce cough*	Honey	Syrup	10 mL	OD
7	Waris, A.	2014	Kenya	Pediatric	URI induce cough*	Honey	Syrup	7.5 mL	TID
8	Herman	2016	Israel	Pediatric	URI induce cough*	Grintuss	Syrup	20 mL	TID
9	Peixoto	2016	Brazil	Pediatric	URI induce cough*	Honey	Syrup	5 mL	OD
10	Parviz	2017	Iran	Pediatric	URI induce cough*	Honey	Syrup	10 mL	TID

Table 16 Honey trial characteristics of intervention formula

No.	Author	Year	Country	Patient	Symptom	Intervention	Formula
1	Ian M. Paul	2007	Hershey	Pediatric	URI induce cough*	Honey	Buckwheat honey 10 mL
2	Shadkam, M. N.	2009	Iran	Pediatric	URI induce cough*	Honey	Natural honey from Kafi-Abad 2.5 mL
3	Cohen, H. A.	2012	Israel	Pediatric	URI induce cough*	Honey	Eucalyptus honey, Citrus honey, Labiatae honey°
4	Raeessi, M. A.	2013	Iran	Adult	Persisting cough	Honey	500 g honey and 70 g Coffee
5	Canciani, M.	2014	Italy	Pediatric	Persisting cough	Grintuss	Grindelia robusta, Plantago lanceolata, Helichrysum italicum, honey°
6	Sopo, S. M.	2014	Italy	Pediatric	URI induce cough*	Honey	Honey 10 mL + milk 90 mL
7	Waris, A.	2014	Kenya	Pediatric	URI induce cough*	Honey	Honey°
8	Cohen, H. A.	2016	Israel	Pediatric	URI induce cough*	Grintuss	Grindelia robusta, Plantago lanceolata, Helichrysum italicum, honey°
9	Peixoto	2016	Brazil	Pediatric	URI induce cough*	Honey	Honey°
10	Ayazi, P.	2017	Iran	Pediatric	URI induce cough*	Honey	Kimia honey and Shahde-Golha honey 10 mL

*Upper respiratory tract infection.

°Not report dose

Table 17 Honey trials characteristic of comparison group

No.	Author	Year	Country	Patient	Symptom	Intervention	Control	Dose
1	Ian M. Paul	2007	Hershey	Pediatric	URI induce cough*	Honey	DM[1], placebo	Children aged 2 to 5 years receiving 8.5 mg/dose (1/2 teaspoon), children aged 6 to 11 years receiving 17 mg/dose (1 teaspoon), and children aged 12 to 18 years receiving 34 mg/dose (2 teaspoons).
2	Shadkam, M. N.	2009	Iran	Pediatric	URI induce cough*	Honey	DM[1], DPH[2], placebo	DM 7.5 mg in 2.5 mL; DPH 6.25 mg in 2.5 L; placebo
3	Cohen, H. A.	2012	Israel	Pediatric	URI induce cough*	Honey	Silan date extract	10 mg
4	Raeessi, M. A.	2013	Iran	Adult	Persisting cough	Honey	Prednisolone, guaifenesin	13.3g of prednisolone; 25g of guaifenesin
5	Canciani, M.	2014	Italy	Pediatric	Persisting cough	Grintuss	Placebo	5 mL
6	Sopo, S. M.	2014	Italy	Pediatric	URI induce cough*	Honey	DM[1], levodropropizine	Dose adjustment by age DM 7.5 mg/dose for aged 2-5 years, 15mg/dose for aged 5-11, and 30 mg/dose for 12-14 years of age. LDP 1 drop/kg until a maximum of 20 drops.
7	Waris, A.	2014	Kenya	Pediatric	URI induce cough*	Honey	Salbutamol, placebo	Salbutamol 2 mg in 5 mL, placebo
8	Cohen, H. A.	2016	Israel	Pediatric	URI induce cough*	Grintuss	Carbocysteine	Carbocyseine 25 mg/kg/day
9	Peixoto	2016	Brazil	Pediatric	URI induce cough*	Honey	Bromelin	5 mL
10	Ayazi, P.	2017	Iran	Pediatric	URI induce cough*	Honey	DPH[2]	Dose adjustment 6.25 mg/dose (2.5 mL) aged 1–6 years, 12.5 mg/dose (5 mL) 6–12 years.

[1]dextromethrophan, [2]diphenhydramine

*Upper respiratory tract infection.

4.3.2.3 Outcome measurements of Honey

The characteristic of outcomes measurements of the studies of honey are reported in **Table 18**. The primary outcome was the global assessment on overall cough symptoms improvement. All trials were assessed by using differences questionnaires such as the 6 trials used 7 points Likert scale for evaluated patient's cough improve. However, questionnaires had four or five questions. Two trials used 4-point Likert scale (0-3 from none to severe) of cough severity and Cough clinical scores with 6-point Likert scale.

The overall with cough improving was answered by patient's parent. Another answered by patient, using telephone, patient's diary, and physician assessed in each visit. In addition changing cough scores before and after treatment was evaluated for each of the parameters: frequency was reported in the six studies, severity was reported in the five studies, cough bothersome was assessed in four studies, child's and parent's sleep were assessed in five studies, the combined cough score (sum of all single items) was assessed in six studies. So, we did subgroup analysis by each outcome to compare of honey effect to relieve cough symptom.

Table 18 Honey included trial of outcome measurement

No.	Author	Year	Country	Patient	Time to follow up (Day)	Tools of assessment	Scale	Outcome measure
1	Ian M. Paul	2007	Hershey	Pediatric	2	Paul questionnaire 2007	7-point Likert scale** (5 items)	CF[1], CS[2]
2	Shadkam, M. N.	2009	Iran	Pediatric	1	Paul questionnaire 2007	7-point Likert scale* (4 items)	CF[1], CS[2], SQC[4], SQP[5]
3	Cohen, H. A.	2012	Israel	Pediatric	2	Paul questionnaire 2007	7-point Likert scale** (5 items)	CF[1], CS[2], BC[3], SQC[4], SQP[5], MS[6]
4	Raeessi, M. A.	2013	Iran	Adult	7	1 question	4-point Likert scale (0-3 from none to severe) of cough severity	CF[1]
5	Canciani, M.	2014	Italy	Pediatric	8	Questionnaire adapted from Chung study 2002	Cough clinical scores with 6-point Likert scale**	MS[6]
6	Sopo, S. M.	2014	Italy	Pediatric	3	Paul questionnaire 2007	7-point Likert scale**	MS[6]
7	Waris, A.	2014	Kenya	Pediatric	5	Paul questionnaire 2007	7-point Likert scale**	CF[1], CS[2], BC[3], SQC[4], SQP[5]
8	Cohen, H. A.	2016	Israel	Pediatric	3	Paul questionnaire 2007	7-point Likert scale**	CF[1], CS[2], BC[3], SQC[4], SQP[5], MS[6]
9	Peixoto	2016	Brazil	Pediatric	1	The number of cough episode	5- point scale***	CF[1], CS[2]
10	Ayazi, P.	2017	Iran	Pediatric	2	Persian questionnaire	7-point Likert scale**	CF[1], CS[2], BC[3], SQC[4], SQP[5], MS[6]

*Cough Severity Assessment Questionnaire. Scoring: 0=not at all, 1=not much, 2=a little, 3=somewhat, 4=a lot, 5 = very much, 6 = extremely.

**Cough clinical scores day and night (Modified from Chung 2002) 0= absent, 1=for a short period (approximately a few minutes), only at awakening/only before falling asleep; 2=for 2 short periods (approximately 10 minutes), Awaken once/early awaken due to cough; 3=Frequent cough that does not interfere with normal activities, frequently awaken due to cough; 4=Frequent cough that interferes with normal activities, frequent cough for the most part of the night; 5=disturbing cough for the most part of the day, disturbing cough.

***0=absent; 1=mild, 2=moderate; 3=intense; 4=very intense

[1]CF: cough frequency

[2]CS: cough severity

[3]BC: child sleep score

[4]SQC: parent sleep score

[5]SQP: cough bothersome

[6]MS: mix score of cough.

4.3.2.4 Effect estimates of honey for reduce cough

The effect estimates of honey measured by comparing as 3 aspects included:

1. between honeys versus placebo,
2. between honeys versus active control
3. between honey formulation as monotherapy and mix with other herbs

Honey versus placebo was compared with six outcomes included cough frequency (CF), cough severity (CS), sleep quality children (SQC), sleep quality parent (SQP), number of study comparisons with five studies (67, 71, 72, 74, 76, 78) and outcome with bothersome cough (BC) in two studies (Cohen, H. A.2012, Waris, A.2014), and mix scores of cough (MS) (Cohen, H. A.2012, Canciani, M.2014). Data analysis are shown in **Figure 7**. Six trials showed a statistically significant effect in favour of honey compared to placebo in cough severity (P <0.05) and although significant heterogeneity was found in the original study results (n = 605, SMD: -0.60, 95%CI [-1.21 to 0.00], I^2 =85.2%, P<0.0001), sleep quality of children (P < 0.0001) and although no significant heterogeneity was found in the original study results (n = 545, SMD: -0.84, 95%CI [-1.2 to -0.46], I^2 =36.8%, P=0.191), Sleep quality parent (P < 0.0001) and although no significant heterogeneity was found in the original study results (n = 545, SMD: -0.80, 95%CI [-1.04 to -0.55], I^2 =0 %, P=0.629). The included trials data analysis were shown no significant effect in cough frequency (P=0.095) and although significant heterogeneity was found in the original study results (n = 605, SMD: -0.55, 95%CI [-1.20 to 0.09], I^2 =84.1%, P<0.001), bothersome cough (P =0.07) and although no significant heterogeneity was found in the original study results (n = 576, SMD: -0.53, 95%CI [-1.12 to 0.06], I^2 =0 %, P=0.915), and mix overall scores of cough not found statistic significant (P =0.368) and although no significant heterogeneity was found in the original study results (n = 476, SMD: -0.99, 95%CI [-3.14 to 1.16], I^2 =26.2 %, P=0.258). Finally, overall effective summary outcome was found a statistic significant all studies included (n = 3252, SMD: -0.63, 95%CI [-0.85 to -0.40], I^2 =0 %, P<0.0001).

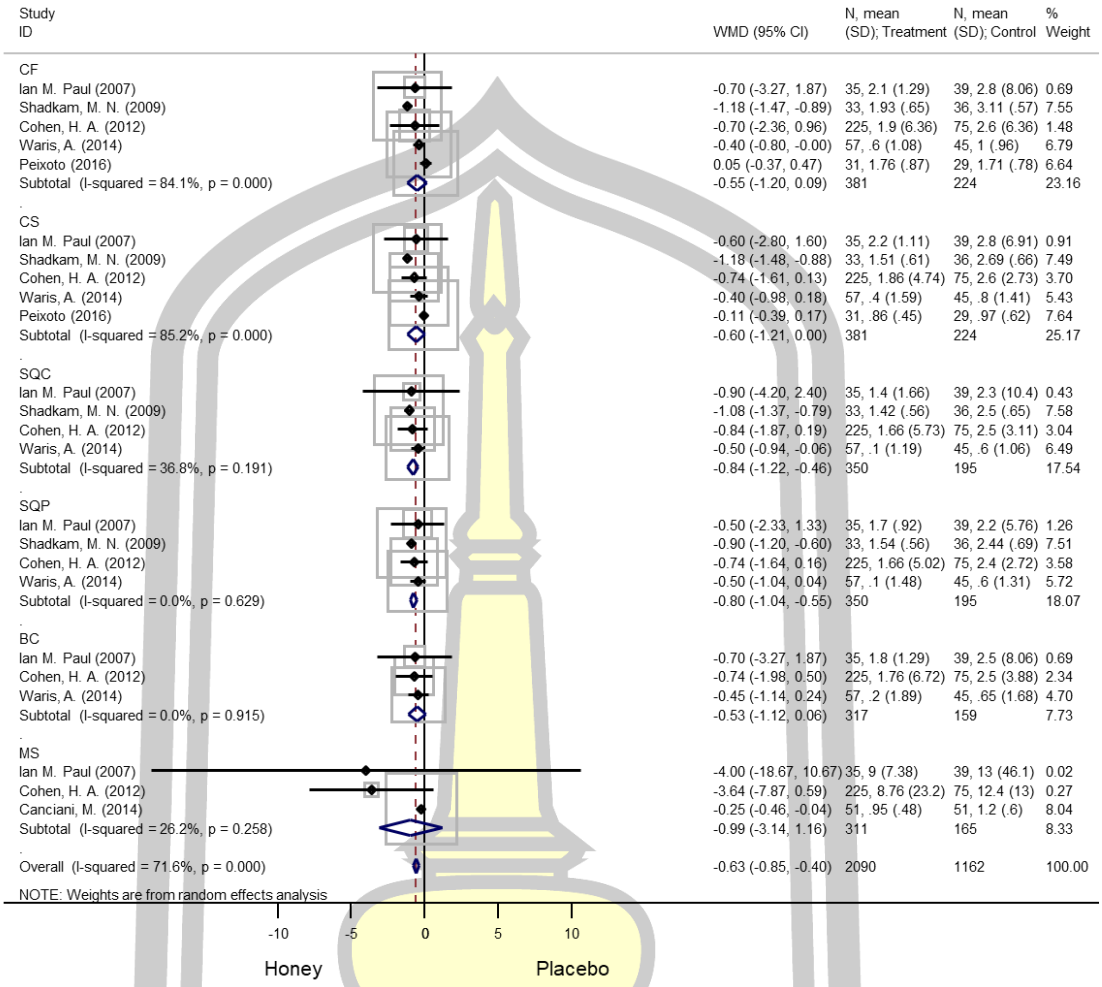


Figure 6 Honey versus placebo as measured cough improvement score

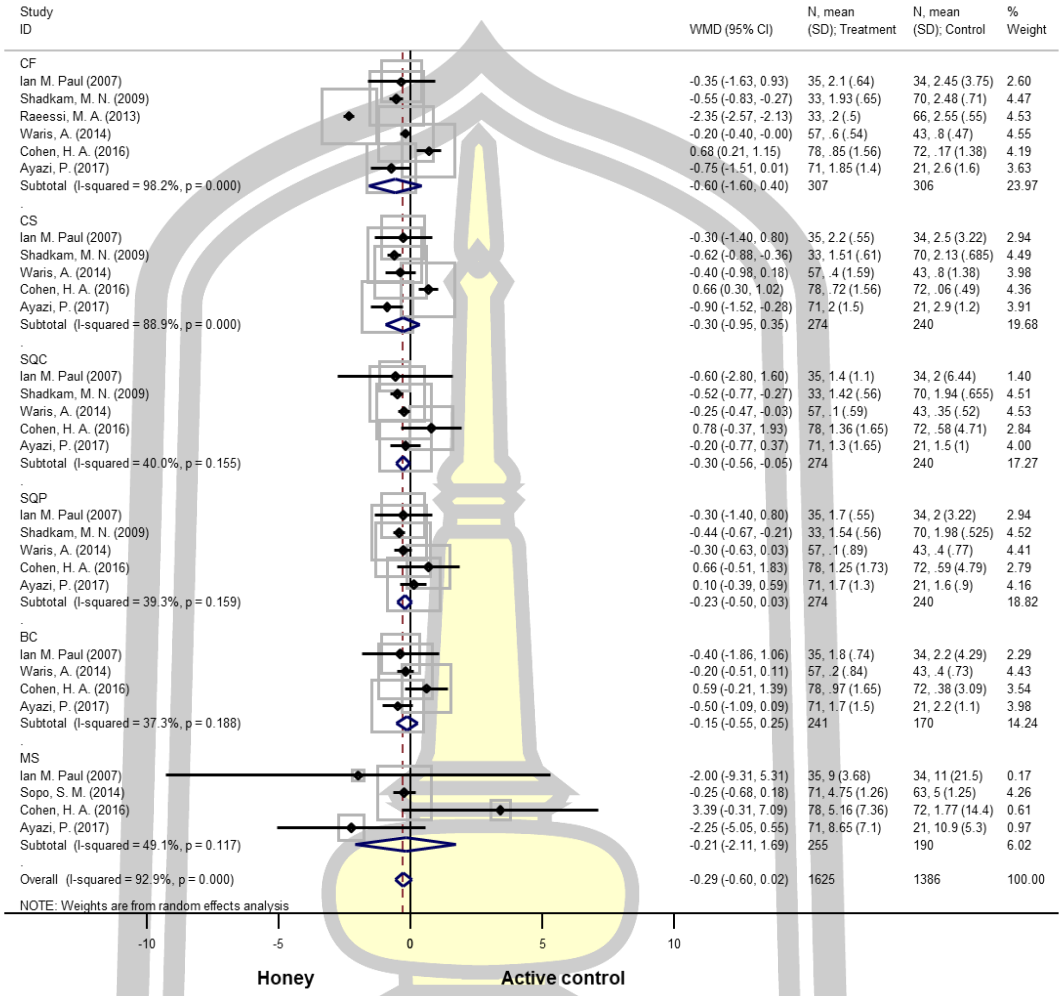


Figure 7 Honey versus active control as measured cough improvement score

Data analysis are shown in **Figure 8**. Honey versus active control was compared with six outcomes and six studies included in meta-analysis. Active control included dextromethorphan, diphenhydramine, prednisolone, guaifenesin, levodropropizine, salbutamol, carbocysteine. Evidences from six trials showed a statistically significant effect in favour of honey compared to active control in sleep quality of children (P = 0.02) and although no significant heterogeneity was found heterogeneity in the original study results (n = 514, SMD: -0.30, 95%CI [-0.56 to -0.05], I^2 =40%, P=0.155). The included trials data analysis showed no significant effect in cough frequency (P=0.36) and although significant heterogeneity was found in the original study results (n = 514, SMD: -0.30, 95%CI [-0.95 to 0.35], I^2 =88.9%,

P<0.001), cough severity (P=0.24) and although significant heterogeneity was found in the original study results (n = 613, SMD: -0.60, 95%CI [-1.60 to 0.40], I^2 =98%, P<0.001), sleep quality of parent (P =0.08) and although no significant heterogeneity was found heterogeneity in the original study results (n = 514, SMD: -0.23, 95%CI [-0.50 to 0.03], I^2 =39.3 %, P=0.159), bothersome cough (P =0.45) and although no significant heterogeneity was found heterogeneity in the original study results (n = 411, SMD: -0.15, 95%CI [-0.55 to 0.25], I^2 =37.3 %, P=0.188), and overall scores of cough not found statistic significant (P =0.83) and although no significant heterogeneity was found moderate heterogeneity in the original study results (n = 466, SMD: -0.21, 95%CI [-2.11 to 1.69], I^2 =49.1 %, P=0.117). Finally, overall effective summary outcome was found no statistic significant in all studies included (P=0.07, n = 3,111, SMD: -0.29, 95%CI [-0.60 to 0.02], I^2 =93 %, P<0.0001).

In order to subgroup specifically of each active control included diphenhydramine (DPH) in **Figure 9** and we analysed subgroup between each of medication group. Evidences from two trials showed a statistically significant effect in favour of honey compared to DPH in cough frequency (P<0.001) and although no significant heterogeneity was found in the original study results (n = 159, SMD: -0.60, 95%CI [-0.90 to -0.30], I^2 = 0%, P=0.669), cough severity (P < 0.001) and although no significant heterogeneity was found in the original study results (n = 159, SMD: -0.66, 95%CI [-0.94 to -0.38], I^2 = 0%, P=0.396), sleep quality children (P =0.002) and although no significant heterogeneity was found in the original study results (n = 180, SMD: -0.47, 95%CI [-0.76 to -0.18], I^2 = 12.8%, P=0.284). While sleep quality of parent (P = 0.426) with significant heterogeneity was found moderate heterogeneity in the original study results (n = 159, SMD: -0.17, 95%CI [-0.79 to 0.33], I^2 =76.3 %, P=0.061), and overall effective summary outcome were not found no statistic significant in all studies included (P<0.001, n = 3, 111, SMD: -0.50, 95%CI [-0.65 to -0.35], I^2 =18.5 %, P=0.273).

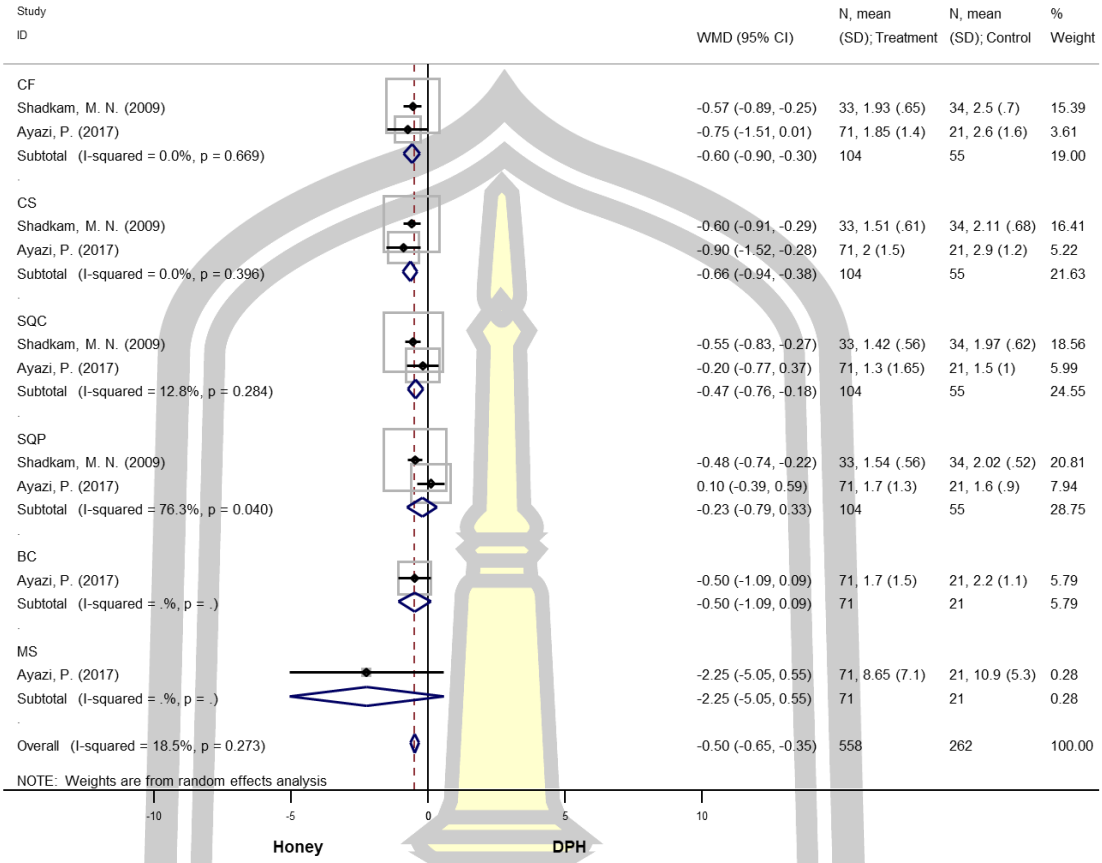


Figure 8 Honey versus DPH as measured by cough improvement score

In order to subgroup specifically of each active control included dextromethorphan (DM) and we analysed subgroup between each of medication group, we showed data analysis in **Figure 10**. Evidences from three trials showed a statistically significant effect in favour of honey compared to DM in cough frequency (P=0.001) and although no significant heterogeneity was found in the original study results (n = 138, SMD: -0.53, 95%CI [-0.84 to -0.22], I^2 = 0%, P=0.778), cough severity (P < 0.001) and although no significant heterogeneity was found in the original study results (n = 138, SMD: -0.62, 95%CI [-0.92 to -0.33], I^2 = 0%, P=0.547), sleep quality of children (P= 0.001) and although no significant heterogeneity was found in the original study results (n = 138, SMD: -0.49, 95%CI [-0.78 to -0.20], I^2 = 0%, P=0.922), sleep quality of parents (P= 0.002) and although no significant heterogeneity was found in the original study results (n = 138, SMD: -0.39, 95%CI [-0.65 to -0.14], I^2 = 0%, P=0.862), and overall scores of cough statistic significant was not found (P =0.968) and although no significant heterogeneity was

not found in the original study results (n = 135, SMD: -0.01, 95%CI [-0.56 to -0.54], I^2 = 0%, P=0.593). Finally, overall effective summary outcome was found a statistic significant (P<0.001) all studies included (n = 756, SMD: -0.47, 95%CI [-0.61 to -0.33], I^2 =0 %, P=0.893).

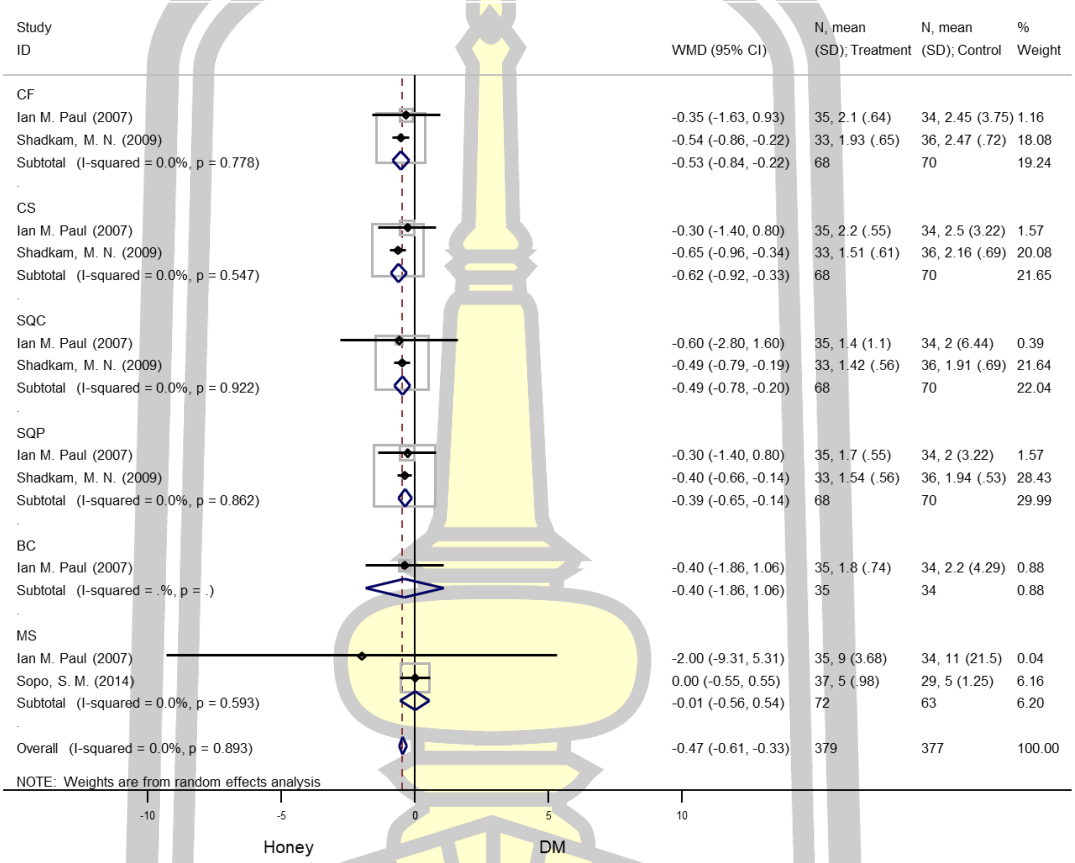


Figure 9 Honey versus DM as measured by cough symptom improvement score

4.3.2.5 Adverse events of Honey

Four of ten studies (Raeessi, M. A.2013, Sopo, S. M.2014, Peixoto.2016, Ayazi,P. 2017) did not report data of side effect or adverse events after used experimental intervention. The author (Peixoto.2016) explained the frequency of reported adverse events, such as episodes of vomiting, epi-gastric and abdominal pain, among others. The monitoring of subsequent adverse events was not performed. And three studies did not report the process for monitor study intervention. Six studies assessed and followed up. Safety data are presented in **Table 19**.

The six trials reported adverse events more than one symptom from their study and we evaluated and subgroup symptom such as GI side effect included nausea, vomiting, diarrhoea, stomach-ache, and abdominal pain, rash, nervousness, and drowsiness. Data are shown in **Figure 11**. Meta-analysis from most studies showed data of safety of experimental medication and control was a statistic significantly in nervousness events (n = 9/247, RR: 6.63, 95%CI [1.63, 27.05], P-value= 0.008), with no heterogeneity in these results (I^2 = 0%; P = 0.524), for drowsiness event was shown from three studies, and showed no significant (n = 6/397, RR: 0.75, 95%CI [0.10, 5.66], P-value= 0.784), with low heterogeneity in these results (I^2 = 24.1%; P = 0.268), GI event result from five studies showed no statistic significant (n = 150/807, RR: 1.28, 95%CI [0.70, 2.36], P-value= 0.425), with high heterogeneity in these results (I^2 = 70%; P = 0.008), and rash event from two studies showed no statistic significant (n = 7/295, RR: 0.54, 95%CI [0.10, 2.96], P-value= 0.476), with no heterogeneity in these results (I^2 = 0%; P = 0.624).

Figure 10 Adverse events from Honey intervention

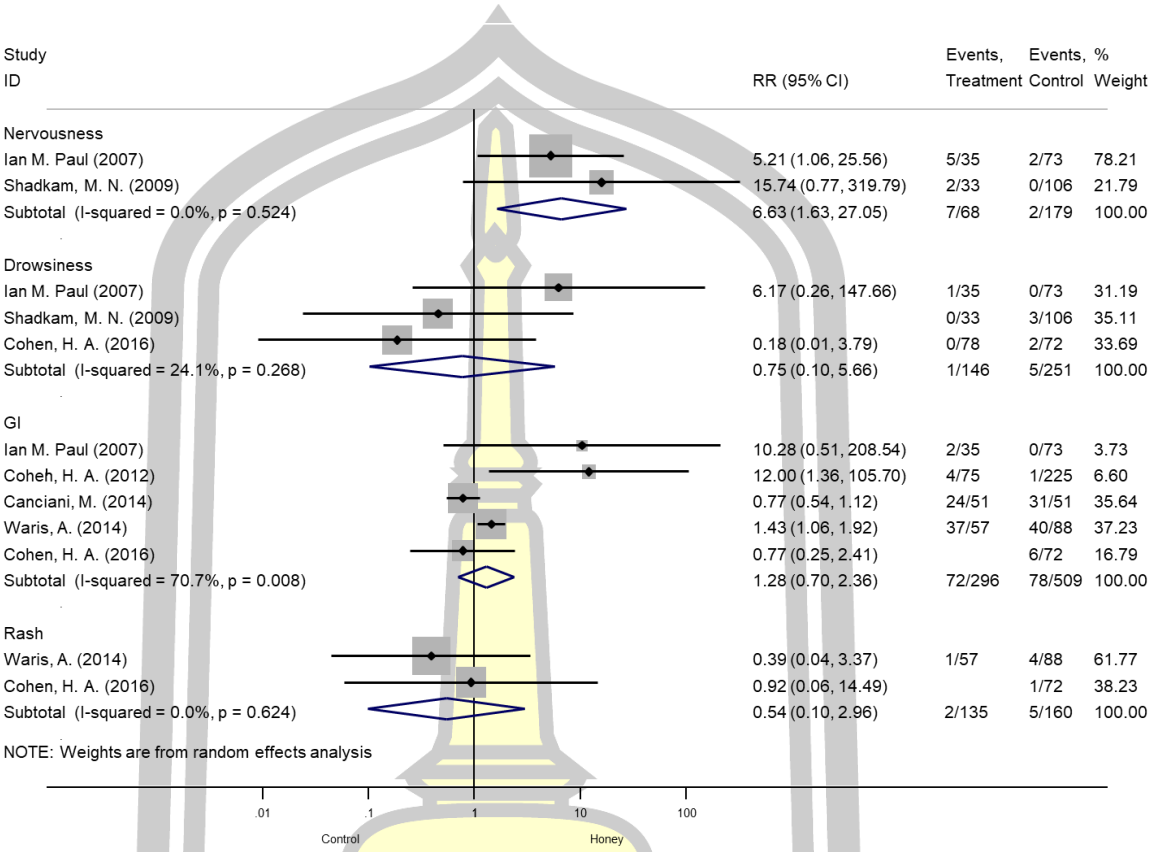


Table 19 Honey characteristic of adverse event data

No.	Author	Year	Country	Study design	Age	Patient	Intervention	Control	Adverse event
1	Ian M. Paul	2007	Hershey	RCT	2-15	Pediatric	8	2	Nervousness, drowsiness, GI*
2	Shadkam, M. N.	2009	Iran	RCT	2-8	Pediatric	2	5	Nervousness, drowsiness, otitis
3	Cohen, H. A.	2012	Israel	RCT	2-18	Pediatric	4	1	GI*
4	Raeessi, M. A.	2013	Iran	RCT	2-5	Adult	0	0	No information
5	Canciani, M.	2014	Italy	Multi-centre, RCT placebo	1-5	Pediatric	24	31	GI*
6	Sopo, S. M.	2014	Italy	Open-label; RCT	>=18	Pediatric	0	0	No information
7	Waris, A.	2014	Kenya	RCT	3-6	Pediatric	44	54	Hand tremor, rash, tachycardia, GI*
8	Cohen, H. A.	2016	Israel	Multi-centre, RCT single-blinded.	2-14	Pediatric	6	9	Rash, drowsiness, GI*
9	Peixoto	2016	Brazil	Pragmatic, double-blind, RCT, parallel-group	1-12	Pediatric	0	0	No information
10	Ayazi, P.	2017	Iran	RCT	2-5	Pediatric	0	0	No information

GI* patients presented with symptom such as nausea, vomiting, abdominal pain, diarrhea, stomachache.

4.3.3 *Zingiber officinale* (Ginger)

4.3.3.1 Ginger trials characteristic

After searching 17 studies and after screen abstract, the 3 studies (80-82) included in our study. Three trials were reported between since 2007-2014. Characteristic of 3 trials are presented in **Table 20**. The 2 trials are from The United Kingdom (80, 81), and the last one is from China (82). Two trials were randomize control placebo control trial and one study was placebo control trial and cross-over study, and two studies were double blind study. Patients included in all trials were adult and diagnosis with asthma, chronic obstructive pulmonary disease and influenza, patient age ranges 18 to 65 years old. 545 participants were included, 222 are males and 323 are the females. Patients included criterias in study 2007 are patient with persisting asthma had a documented positive bronchodilator reversibility test with ≥ 15% improvement in FEV1 from 15 to 30 minutes after inhalation of at least 200 µg of salbutamol (beta-2-adrenergic agonist administration) or documented PEF variability of 20%. In study 2014 included all patients, who had a diagnosis of obstructive lung disease and non-reversible airflow limitation, as defined by a post-bronchodilator ratio of forced expiratory volume, patient with smoker were included. And final study reported their inclusions criteria patients is diagnosis within influenza like illness by physician.

Exclusion criteria of study of Thomas. M. 2007 (81) was explained the documented COPD and unstable asthma defined the requirement for oral corticosteroids and/or admission to hospital for asthma (including treatment in an emergency room) in the prior three months. Study of Brockwell, C. 2014 (80) included patient with COPD and excluded patient, who receives oral corticosteroids, seasonal disease, or an exacerbation or recent change in maintenance therapy within 6 weeks before came to study. Patients are unable to discontinue short-acting β-agonists for at least 4 hours, long-acting β-agonists for 12 hours, or tiotropium for 48 hours before study going on visit 2 (before week 4), and Wanglei (2010) (82) focuses in patient who had any treatment onset for influenza like illness, other confirm with upper respiratory viral or bacterial infection, pregnancy, history with herbs in experimental medication allergy, all patients, who had alcoholism and drug abuser,

sever disease with cardiovascular, respiratory, cancer, CNS, hepatic, renal, HIV, and patient receiving steroid or immune suppressants or having been vaccinated of influenza previous 12 months.

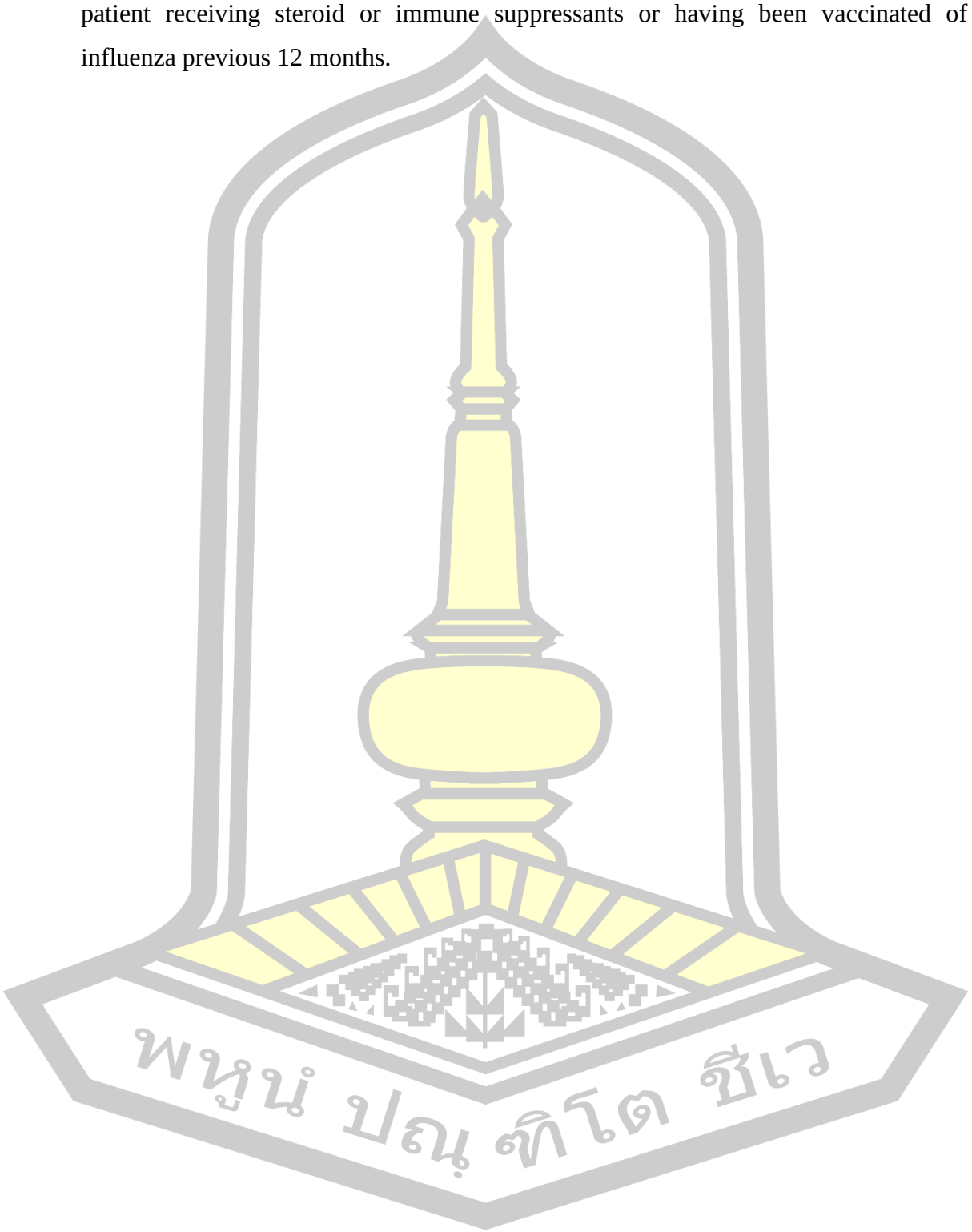


Table 20 Ginger trials characteristic

No.	Author	Year	Country	Study design	Sample sizes		Age	Sex		Patient	Disease	Treatment duration (days)
					Intervention	Control		Male	Female			
1	Thomas, M.	2007	UK	RCT, cross over trial	16	16	18-75	7	25	Adult	Asthma induce cough	252
2	Wang, Lei	2010	China	RCT ; placebo-controlled study	360	120	18-65	189	278	Adult	Influenza induce cough	3
3	Brockwell, C.	2014	UK	RCT ; placebo-controlled study, singer blind	20	13	>18	19	14	Adult	COPD persistent cough	7

4.3.3.2 Ginger characteristic of intervention

Ginger are used an herbal mixture in combination with other herbs as the interventions. **Table 21** presents the characteristics of ginger study in the included trials. Out of the 3 trials explained about ginger to experimental intervention and compared with placebo or standard treatment.

All studies used ginger mixture with other herbs (AKL1) that was produced according to UK Good Manufacturing Practices. AKL1 capsules is contains a synthetically-derived phytochemical component of *Picrorrhiza kurroa, apocynin*, together with *Picrorrhiza kurroa, Zingiber officinale* and a standardized extract of *Ginkgo biloba*. The plant materials have been standardized against a known phytochemical marker, and additionally each ingredient was cross evaluated by the Medicinal Chemistry Department at the University of Utrecht to guarantee to standardization content as: Ginkgo biloba (standardized to contain ginkgo flavone glycosides minimum 24%), *Zingiber officinale* (standardized to contain gingerols minimum 5%), *Picrorrhiza kurroa* (enriched to contain apocynin minimum 30%). Each 500 mg AKL capsule, which is a patented formulation, contains: Picrorrhiza kurroa (enriched to contain apocynin 28%) 270 mg, *Ginkgo biloba* (standardised to contain ginkgo flavone glycosides 24%) 130 mg, *Zingiber officinale* (standardised to contain gingerols 5%) 100 mg. Study 2010 was used antiwei 6 g granule that had a standard formula from a traditional Chinese prescription, consisting of Mahuang (Herba Ephedra) 10.99%, Bai mao geng (*Rhizoma Imperatae*) 32.68%, Gegen (Radix puerariae)16.48%, Guizhi (*Ramulus Cinnamoumum*) 10.99%, Ku xing ren (*Semen Armeniacae Amarum*.) 10.99%, Ganjiang (*Rhizoma Zingiberis*) the dried rhizome of *Zingiber offici*nale (wild).Rose. 6.59% and Gancao (*Radix Glycyrrhizae*) 10.99%.

In control group, all studies included placebo and normal treatment. The two studies (80, 81) used AKL1 capsule and one study (82) used antiwei granule comparing with placebo.

Table 21 Ginger trial characteristic of intervention

No.	Author	Year	intervention	Formula	Placebo	Dose
1	Thomas, M.	2007	AKL 1 500 mg	*Ginkgo biloba* (ginkgo flavone glycosides 24%), *Zingiber officinale* (gingerols 5%), *Picrorrhiza kurroa* (apocynin 30%). Each 500 mg AKL capsule, contains: *Picrorrhiza kurroa* 270 mg, *Ginkgo*130 mg, *Zingiber officinale* 100 mg	Normal subject	BID
2	Wang, Lei	2010	Antiwei 6g	Mahuang (Herba Ephedra) 10.99%, Bai mao geng (*Rhizoma Imperatae*) 32.68%, Gegen (*Radix puerariae*)16.48%, Guizhi (*Ramulus Cinnamoumum*) 10.99%, Ku xing ren (*Semen Armeniacae Amarum*.) 10.99%, Ganjiang (*Rhizoma Zingiberis*) the dried rhizome of Zingiber officinale (wild).Rose. 6.59% Gancao (*Radix Glycyrrhizae*) 10.99%.	Starch and bitter agent	BID
3	Brockwell, C.	2014	AKL 1 500 mg	*Ginkgo biloba* (ginkgo flavone glycosides 24%), *Zingiber officinale* (gingerols 5%), *Picrorrhiza kurroa* (apocynin 30%). Each 500 mg AKL capsule, contains: *Picrorrhiza kurroa* 270 mg, *Ginkgo*130 mg, *Zingiber officinale* 100 mg	Calcium phosphate and magnesium stearate	BID

4.3.3.3 Ginger data outcome assessment

The primary outcome measure of ginger study was the assessment on overall symptoms improvement. All three trials assessed their outcome by using differences tools such as the 2 trials used Leicester cough questionnaire had 7 points Likert scale for evaluated patient's cough improve. However, questionnaires did not tell about how many item they used. And the last study assessed by using patients recorded once daily using a four-point scale (0 absent, 1 mild, 2 moderate, and 3 severe). However, all three trials did not explain their tools or question they asked patient. Finally, all tools used for evaluated patient quality with cough symptom.

4.3.3.4 Adverse events of ginger formula

All the 3 trials assessed the safety by recorded frequency of reported adverse events, monitored blood pressure, full blood count, urine, stool, electrolytes, liver function tests, renal functions and electrocardiogram (ECG).

The 3 trials reported adverse events after patient receives the study medication such as asthma exacerbation in ten patients (5 patients in placebo and 4 patients in experimental group), study 2010 (82) showed adverse events with a patient given Antiwei had mild paroxysmal palpitation and study 2014 (80) showed five patients had adverse events. Chest infections were diagnosed in a patient in each treatment allocation group: one in the placebo group at baseline (visit 2) and one in the AKL1 group at the final visit (visit 4). In the AKL1 group, one patient reported nightmares and one patient had right shoulder pain at the baseline visit, and one patient had influenza at the final visit.

4.3.4 Justicia adhatoda (Malabar nut)

4.3.4.1 Malabar study characteristic

After searching 14 studies and after screening abstract, the 2 studies (83, 84) included in our study and data are shown in **Table 22**. Two trials reported characteristic and published in 2005 and 2015. Both trials are from Armenia. Study design was a randomize control placebo control trial and another study was placebo

control trial, double blind study. Patients included in trials were adult and with URI induce cough, patient's age range from 18 to 65 years old. 267 patients were included, 104 are males and 163 are females. Patients included are patients suffering from cough and acute bronchitis with a positive test for cilia abnormalities, and predominant complaint of the first signs and symptoms of uncomplicated URI (e.g., sore throat, blocked nose, runny nose, hoarseness, cough, headache, and general malaise).

Exclusion criteria are patients who had history of allergies to cut flowers, herbs, or bitter substances; had acute symptoms for over 36 hours or fever of >38.5 °C; were taking antibiotics, anti-inflammatory drugs, or antihistamine; suffered from emphysema, bronchiectasis or pneumosclerosis, persons known to have problems with abuse of medications, narcotics, tobacco or alcohol.

Table 22 Malabar trial characteristics

No.	Author	Year	Country	Study design	Sample sizes		Age	Sex		Patient	Disease
					Intervention	Control		Male	Female		
1	Narimanian, M.	2005	Armenia	RCT	30	60	18-54	28	62	Adult	URI induce cough
2	Barth, A.	2015	Armenia	RCT	66	111	18-65	76	101	Adult	URI induce cough

4.3.4.2 Malabar nut trials of intervention and outcome measurement

Malabar nut was used as an herbal mixture in combination with other herbs. Characteristics of malabar nut in the included trials are presented. The 2 trials explained about Malabar nut to experimental intervention and compared with placebo and standard treatment. All studies used Justicia mixture with other herbs, the product name was KanJangs. In both study 2005 and 2015 explained their experimental intervention, KanJangs was produced according to the Swedish Herbal Institute (Gothenburg, Sweden). KanJang oral solution (batch EX-0307A), was a fixed combination of extracts from leaves of A. vasica L. (15–25 mg/ml), from *Echinacea purpurea L*. (14–20mg/ml) and from Eleutherococcus senticosus Maxim (5mg/ml) that had been standardised to contain 0.2mg/ml of the alkaloid vasicine, 0.8 mg/ml of cichoric acid, and 0.03mg/ml of eleutherosides.

In control group, all studies reported data about control group included placebo capsule and standard treatment. The two studies (Thomas, M.2014, and Wang, Lei 2010) compared Malabr nut mixture formula versus placebo. The author (study 2014) explained study's placebo formula of Echinacea mixture (batch EX-0307A), was a fixed combination of extracts from Echinacea purpurea L. (14–20mg/ml) and from Eleutherococcus senticosus Maxim (5mg/ml) that had been standardised to contain 0.8mg/ml of cichoric acid, and 0.03mg/ml of eleutherosides B and E. The liquid matrix for both test medications contained liquorice, nipagin, nipasol, sorbitol, polysorbate, eucalyptus oil, peppermint oil, coltsfoot leaf aroma, ginger extract and water. The medications were provided in dark glass bottles (500 ml) with a cap, sealing ring and a measuring dosage cup (graduated 5, 10, 15, 20 and 30 ml). The standard treatment from in both studies is bromhexime coated tablets (Berlin-Chemie, Berlin, Germany) containing 8 mg of bromhexine hydrochloride. The primary outcome measurement in both studies was cough frequency by using tools included self-assessment questionnaires completed on a daily basis by VAS scores of parameters 1–9 as determined in the initial baseline questionnaire. For patient assessment, the VAS end points were marked: 0 cm – no improvement, and 10 cm – pronounced improvement, and the last trial 2015 used a fixed scale from 0 to 9, where 0 indicated no cough, 1–3 a mild cough, 4–6 a moderate cough, and 7–9 a severe cough.

4.3.4.3 Efficacy and averse events of Malabar nut intervention

The 2 studies (2005, 2015) presented results in mean and standard difference of scores of improvement cough symptoms, however, they had difference between tools and scale evaluated. The study 2005 showed scores of no improvement cough symptom from baseline, and in study 2015 assessed cough symptom reducing from patient's baseline. So anyway, result from both study 2005 and 2015 had good effect in reduce patient's cough symptom than placebo, and no difference effects from standard treatment.

The adverse events were reported by patients from two studies, no serious adverse events were observed. A total of 12 minor adverse events were observed in 12 patients: 4 in the PL group, 2 in the KJ group, and 6 in the BH group, minor adverse events included pruritus, diarrhea, abdominal pain, and skin rash.

CHAPTER 5
DISSCUSION AND CONCLUSION

5.1 Summary of evidences

All data searched by the author for using a search term such as part of symptoms, combined with the scientific name of 30 herbs in both Thailand and Lao PDR national list of essential medicines. After the searching process finished, we found 1,745 articles to consist with our search terms. However, we found only four kinds of herbs including eucalyptus, honey, ginger, and malabar nut. We did not find the RCT study of 26 kinds of herbs in national list of essential medicines for relieved cough.

Twenty studies came in systematic review. Findings of efficacy and safety for reducing cough symptom are from 6 RCTs for eucalyptus (*Eucalyptus globulus* Labill), 10 RCTs for honey, 3 RCTs for ginger (*Zingiber officinale*), and 2 RCTs for malabar nut (*Justicia adhatoda*).

4,098 participants from 20 RCTs were included both treatment and control group to use with eucalyptus, honey, ginger, and malabar nut, placebo, or other drugs. Adult from 11 studies and children from 9 studies on age between 1-14 years. 1,538 are males and 2,040 are females, and three studies did not report patient gender.

For all trial descripted about symptom of cough causes included acute bronchitis from 3 studies in eucalyptus (*Eucalyptus globulus* Labill) group; upper respiratory infection 12 studies from eucalyptus, honey, and malabar nut. A study reported treatment of ginger (*Zingiber officinale*) for chronic obstructive pulmonary and influenza.(80-82). Summary of effect of four herbs are presented **in Table 23.**

The duration of cough symptom was presented by patient status included time less than one week in 13 studies, more than two weeks in 3 studies, and 5 studies did not report of symptom time. Duration of follow up time in each study was difference such as less than 2 weeks from 17 studies and more than 2 weeks in 2 studies.

Although no serious AE and minor AEs were mainly gastrointestinal symptoms in the included trials, caution is warranted in interpreting safety before comprehensive safety data is available in **Table 24.**

For this reason, systematic reviews and meta-analyses on herbal medicines are increasingly published (85-101) and deemed more important as cumulative clinical evidence of herbal medicine. Our systematic review and meta-analysis provides a critical summary of clinical evidence of *Eucalyptus* for relieving cough symptoms in both children and adult. Our meta-analysis found that *Eucalyptus globulus* and Honey appears to be beneficial and safe for relieving overall cough symptoms.

Previous systematic reviews and meta-analysis studies have reported the herbal's effect in reducing cough symptoms. Wagner 2015(86) reported the effect of essential oil extract from *Eucalyptus* and other herbs; the author included four studies of essential oil from multiple herbs and showed that active treatments improved the severity and frequency of patient's cough symptoms. However, our study provides an update of *Eucalyptus* effects on cough symptom. We included six studies of Eucalyptus and found a positive effect in reducing overall cough symptom scores and all studies showed mild to a moderate adverse events from *Eucalyptus*.

Eucalyptus effect compared versus placebo in two studies on mix cough symptom scores, Eucalyptus can improve patient symptom. However, eucalyptus appropriated for adult patients with acute cough, mixture eucalyptus 10-20% in formulas, in capsule or spray, And o9the dose was vary. The overall risk of bias were at low risk.

Eucalyptus did not difference in cough frequency and severity when compared with placebo, because the number of study, tools assessment, and age of adult and children patient are vary. The formula and the quantity of eucalyptus was told not clear. Overall risk of bias was high risk. However, the effect was on a positive way in a treatment group than placebo.

Adverse events from the intervention were found GI symptoms including nausea, vomiting, diarrhoea, stomachache, gasternal-infection, and abdominal pain. All symptom in GI outcome did not difference between two groups. However, the adverse events reported from all six trials not related from eucalyptus alone because in the intervention formula was mixture of eucalyptus and other herbs such as *Pinus spp* (pine), *Citrus aurantifolia* (lime), Rosmarinus officinalis, and *Origanum syriacum*.

Oduwole 2015 (100) study the honey effect for relieved cough by systematic review and meta-analysis since 2014 to 2018. In the study 2014 they included three studies and the study 2018 updated six studies. They found the effect of honey can reduce cough symptom when compared with placebo and standard treatment. Other that the author reported no difference of adverse events between this intervention and control groups. In our study, we included ten studies, in children 9 studies and a study in adult. Intervention was pure and mixture honey in syrup form. The data analysis showed that honey can improve patient quality of sleeping and other outcomes when compared with placebo. When compared honey with total active control, no difference was found, except DPH. Honey can reduce cough frequency more than DPH.

The data analysis of honey effect from six studies were compared pure and mixture versus placebo on cough frequency, cough severity, quality of child sleeping, quality of parents sleeping, bothersome cough, and mix cough symptom scores. The data showed honey effect that can improve patient's cough severity and quality of sleeping. However, the tools for assessment are vary between studies in measuring outcomes such as CF, CS, MS. All outcomes had positive way in reduced acute cough in children, and almost studies used honey syrup.

The data analysis of honey effect from seven studies were compared pure and mixture versus active control or standard treatment on cough frequency, cough severity, quality of child sleeping, quality of parents sleeping, bothersome cough, and mix cough symptom scores. The data showed honey can improve patient's all cough symptom and no difference with standard treatment. In mixture formula may have effects from other herbs that mixed with honey. In case, the data analysis subgroup with honey compared to DPH and DM. Honey can reduce cough than two standard medicine in CF, CS, SQC, and SQP. Honey form are in syrup and jam.

6 Adverse event of honey is nervousness symptom. However, the adverse events are reported from all six trials but not related from honey alone because in the intervention formula was mixture between honey and other herbs.

Our study were new update data for honey used for cough, compared with study 2014 and 2018. (93, 100) Our study included 10 trials, all studies were using

honey including pure and mixture with other herbs, study 2018 updated from study 2014, the author included 6 trials. Honey benefit, study 2018 recommend probably relieves cough symptoms to a greater extent than control group and our data result was similar. Effect of honey was better when we compared with placebo but no difference with standard treatment. If we focused on each standard medication, we found honey have good benefit when compared with DM.

Moreover, Oduwole (2018) suggests that more RCTs on the use of honey in the treatment of cough in children are needed. In the present study, honey was effective in relieving most aspects of cough-related symptoms in children and their parents. (86)

No serious adverse events were reported in any of the treatment groups. Non-severe adverse events such as stomachache, nausea, and vomiting were probably more common in the honey groups than no-treatment and placebo groups, but similar with dextromethorphan, diphenhydramine, and salbutamol groups. There was probably a few or no difference in numbers of events in the honey, no-treatment, placebo, dextromethorphan, diphenhydramine, and salbutamol groups for non-severe adverse events such as rash and tachycardia.

Table 23 summary of data analysis effect from interest interventions in four herbs

Herbs finding	Number of study	Intervention interest	Comparable	Form	Dose range	Main result
Eucalyptus globulus Labill	6	Eucalyptus	Control	Capsule Syrup Spray	200-300 mg 10 mL 60 mcg	RR: 1.40, 95%CI [1.19, 1.65], **P-value< 0.0001**
		Eucalyptus	Active control: cefuroxime, ambroxol.	Capsule	300 mg QID	RR: 1.20, 95%CI [0.93, 1.12], **P-value= 0.688**
Honey	10	Honey mono or mixture	Control	Syrup	2.5-10 mL	SMD: -0.63, 95%CI [-0.85 to -0.40], **P-value<0.001**
		Honey mono or mixture	Active control: DM, DHP, prednisolone, guaifenesin, levodropropizine, salbutamol, carbocysteine	Syrup	2.5-20 mL	SMD: -0.29, 95%CI [-0.60 to 0.02], **P-value=0.07**
		Honey mono or mixture	DM, DHP	Syrup	2.5-10 mL	SMD: -0.47, 95%CI [-0.61 to -0.33], **P-value<0.001** SMD: -0.50, 95%CI [-0.65, -0.35] **P-value<0.001**
Zingiber officinale	3	Ginger mixture herbs	Active control Control	Capsule	500 mg, 300 mg BID	Found limited evidence supporting
Justicia adhatoda	2	Malabar mixture herbs	Active control: Bromhexime Control	Solution	5-30 mL	Found limited evidence supporting

Table 24 summary of data in adverse events from herbs intervention

Herbs finding	Number of study	Intervention interest	Comparable	Form	Dose range	AEs
Eucalyptus globulus Labill	6 SR MA: 5	Eucalyptus	Control	Capsule Syrup Spray	200-300 mg 10 mL 60 mcg	**GI symptom** (RR: 1.02, 95%CI [0.33, 3.14]) I^2 = 36.9%; P = 0.191
		Eucalyptus	Active control: cefuroxime, ambroxol.	Capsule	300 mg QID	Moderate intensity Heart burn
Honey	10 SR MA: 10	Honey mono or mixture	Control	Syrup	2.5-10 mL	**Nervousness event** (RR: 6.63, 95%CI [1.63, 27.05], I^2 = 0%) P-value= 0.008 **Drowsiness event** (RR: 0.75, 95%CI [0.10, 5.66], I^2 = 24.1%) P-value= 0.784 **GI event** (RR: 1.28, 95%CI [0.70, 2.36], I^2=70%) P-value= 0.425 **Rash event** (RR: 0.54, 95%CI [0.10, 2.96], I^2 = 0%) P-value= 0.476
		Honey mono or mixture	Active control: DM, DHP, prednisolone, guaifenesin, levodropropizine, salbutamol, carbocysteine	Syrup	2.5-20 mL	
		Honey mono or mixture	DM, DHP	Syrup	2.5-10 mL	
Zingiber officinale	3 No SR MA	Ginger mixture herbs	Active control Control	Capsule	500 mg, 300 mg BID	Asthma exacerbation Mild paroxysmal palpitation Chest infection Nightmares, pain, influenza
Justicia adhatoda	2 No SR MA	Malabar mixture herbs	Active control: Bromhexime Control	Solution	5-30 mL	Pruritus, diarrhea, abdominal pain, skin rash 10.5%

Ginger and malabar nut did not have enough evidences to support effect in pure herb for reduced cough. Traditionally, malabar has been used for the treatment of bronchial disorders such as acute and chronic cough, bronchitis and asthma, and also as an expectorant in the treatment of acute and chronic bronchial. Constituents of study product has been shown to have anti- stress effects, which might be occasioned partly by an endocrine and partly by an immunomodulatory mechanism of action (102).

In Thailand and Lao PDR used difference kind of herbs was remedies cough symptom, included 30 kind of herbs in difference formula. Our study found evidences of four herbs included eucalyptus in Lao PDR drug list and honey, ginger, malabar nut in Thai national drug list.

In current treatment, we used eucalyptus in our local within mixed herbs and difference dose. The most evidences supported eucalyptus had effective with antimicrobial (103). Eucalyptus in capsule, syrup, and spray dose 2-10 mL using in adult than children for reducing cough symptoms. Safety were reported mild to moderate GI symptoms, when patient used eucalyptus, however, we can monitor these symptoms.

Our study are first review of ginger and malabar nut used for reduce cough, the effect of these herbs were no difference with control group. Cause of these effect as diseases, patient included conditions, amount of ginger extract in intervention formula, and the importance number of study included trial were limited data.

5.2 Strengths and limitations

This is a meta-analysis of herbal medicine suggest herbs used in Thai and Lao essential national drug lists as a remedy for cough symptoms. The overall risk of methodological bias in the reviewed studies was low. The main challenge was to select the conditions to be included in the review since cough symptoms have many complex causes. Another limitation was study data. For example, high risk of bias in missing outcome data domain, cause of these from patient dropout more than 10%, some study we don’t have any responds from the author for their outcome not presented.

5.3 Implications for clinical practice and development

A number of high-quality studies show that herbals preparations containing eucalyptus and honey improve overall cough symptoms included cough frequency, cough severity, bothersome cough, sleep quality for children and parent, and mix overall symptoms of cough with few mild adverse effects.

With better to eucalyptus receive a month in bronchitis and 3 days intakes in URI induce cough symptom of a preparation constraining such as Myrtol® capsule 1.2g per day seem to be adequate for adults to alleviate patients' cough and aromatic herbs spray appears adequate to alleviate patients' cough symptoms included mix overall cough scores in adult. Eucalyptus had good effect for reducing cough frequency used in URI and acute bronchitis induce cough in adult and children. Eucalyptus present a few ADRs and we can monitor this side effects.

In case of URI induce cough and persistence cough, honey base preparation can be recommend for reducing cough frequency, cough severity, bothersome cough, overall of cough symptom and improving quality of sleeping in children and parent, on 7 days. Honey appropriated use in children and dosage require adjustment.

Study with ginger in mixture with other herbs can't seem difference with other treatment in asthma and COPD induce cough, may come from herbs formula, and condition of disease.

5.4 Implications for future research

Our systematic review and meta-analysis found compelling for four herbs included eucalyptus, honey, ginger, and malabar. The evidences for the effectiveness of herbs used for relief cough in Thailand and Lao PDR national list of essential medicine. Future studies focusing on disease-specific cough will be more helpful to provide information that is clinically more relevant. Other herbs in both country national list of essential medicine should be prioritized for the next trials because there are few effective treatment options.

The risk of bias in part of systematic reviews cannot be reliably evaluated from published papers if reporting on important methodological aspects is well but had high risk in measurement outcome domain.

Further research is needed to compare complementary/alternative approaches with conventional pharmaceuticals for cough symptoms in order to evaluate the potential of herbal remedies as supplement or even alternative to conventional treatment. Need more evidences such as clinical trial about use herbs in human.

5.5 Conclusion

This review found four herbs from 30 herbs in national list of essential medicine from Thailand and Lao PDR including eucalyptus, honey, ginger, and malabar nut. The risk of bias included trial are poor in missing outcome data. Eucalyptus and honey preparations were significantly superior to placebo in alleviating the overall symptom of patients' cough and improved patient quality of life. These herbal medicines may be recommended as alternatives or adjunct to conventional medicine. Ginger and malabar nut will need more evidences to support this effect. Additional research, including other herbal treatments, is needed in this area. We found positive effect similar to standard treatment.

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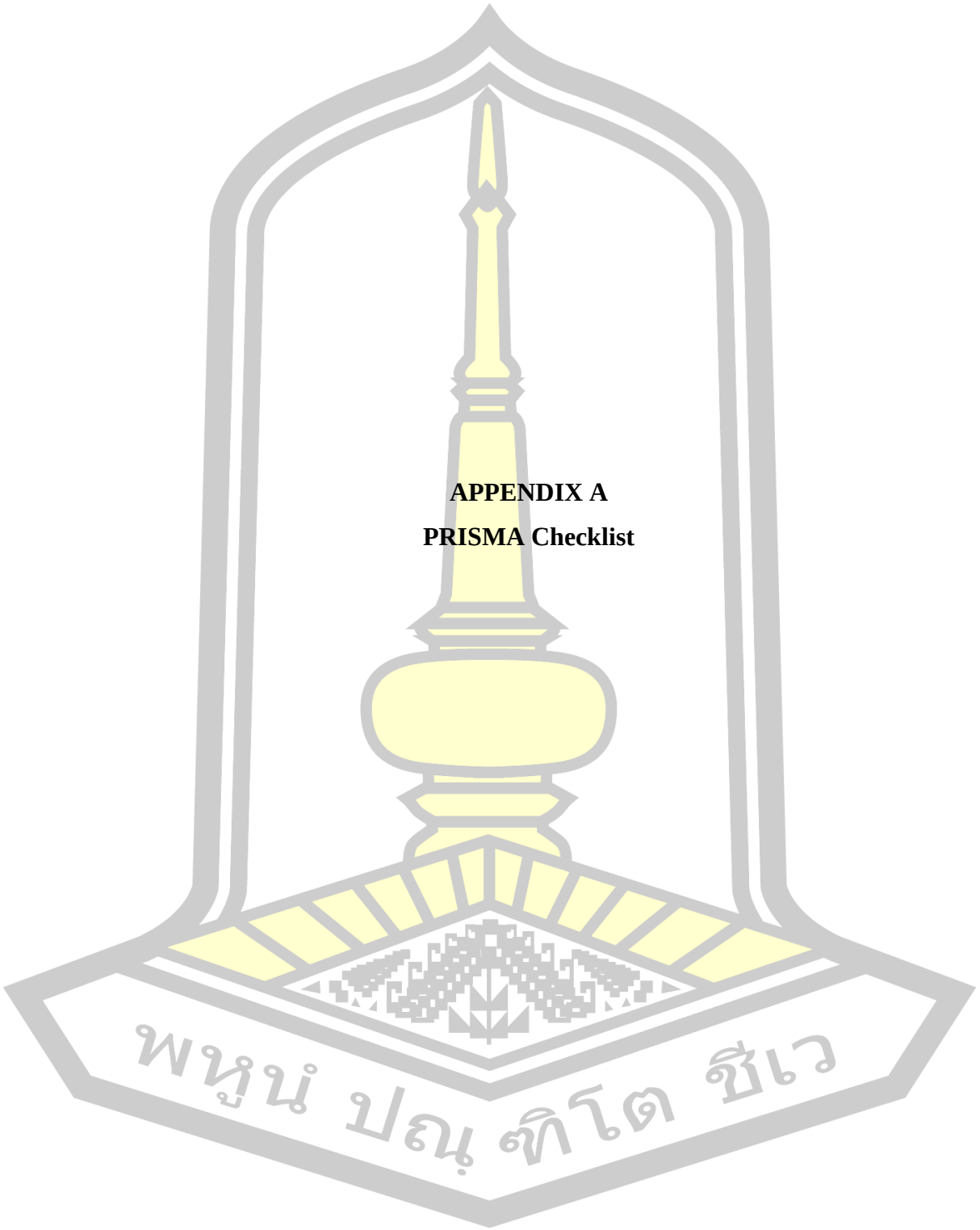
APPENDIX



APPENDIX A

PRISMA Checklist

PRISMA checklist

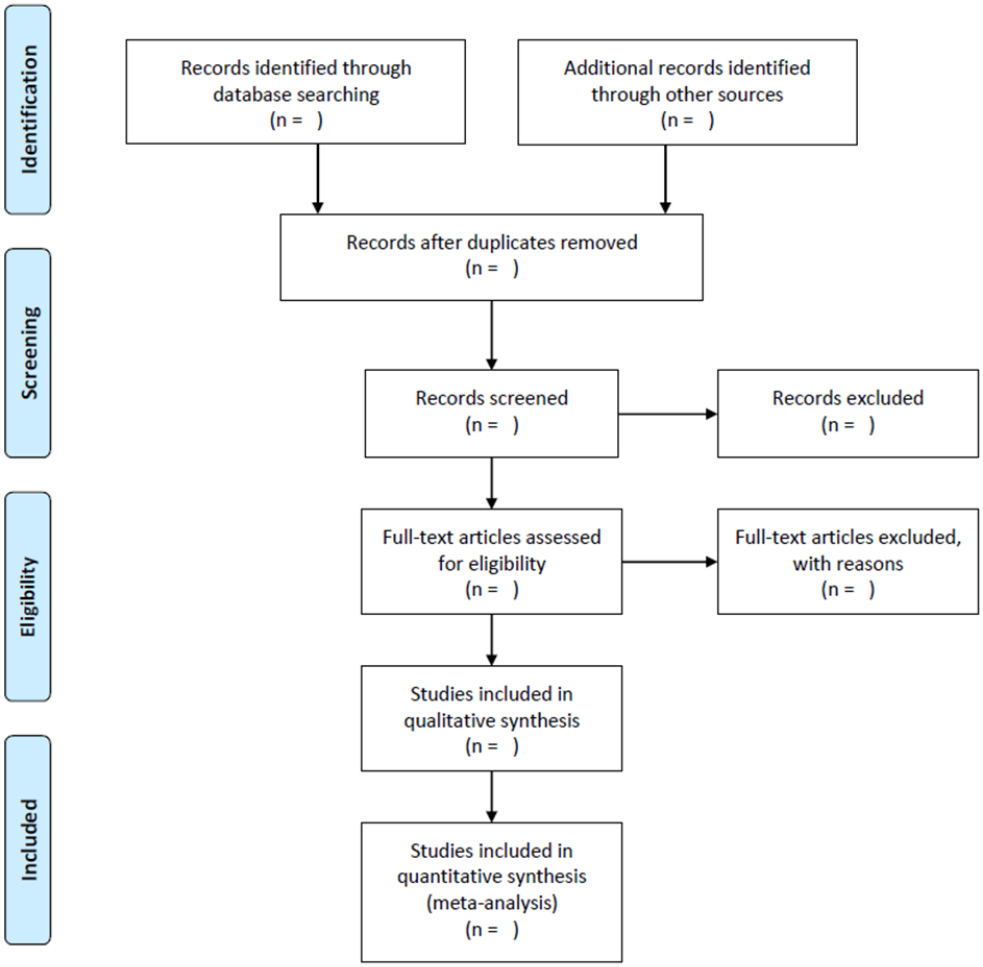
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

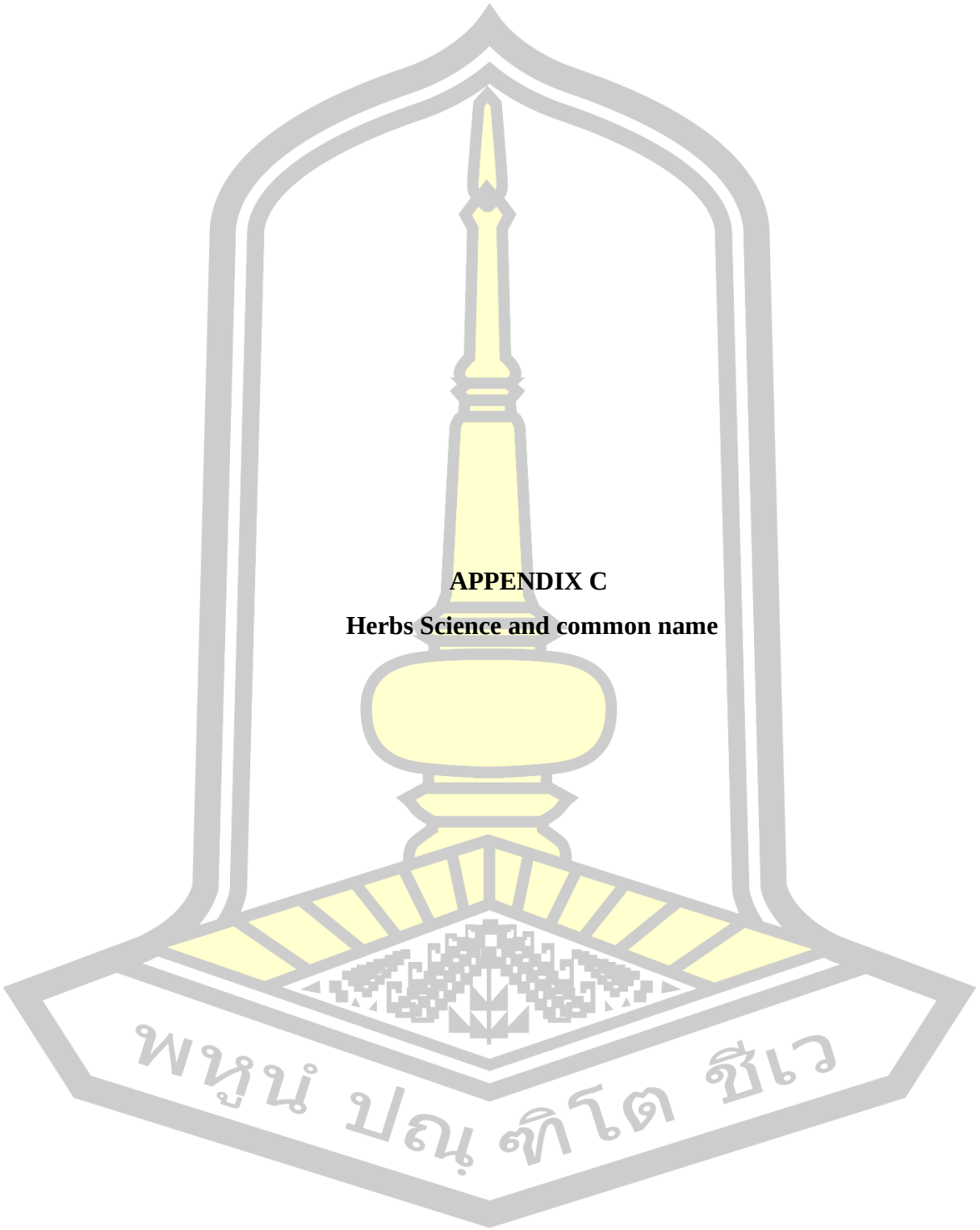
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

APPENDIX B

PRISMA diagram

PRISMA Flowchart diagram





APPENDIX C

Herbs Science and common name

Herbs Science and common name

Number	Name	Scientific name
1	ยูคาลิปตัส	*Eucalyptus globulus* Labill
2	มะขามป้อม	*Phyllanthus emblica* L
3	ชะเอมเทศ	*Glycyrrhiza glabra*
4	สะระแหน่	*Mentha x cordifolia* opiz ex fresen
5	สมอพิเภก	*Terminalia bellirica*
6	มะนาว	*Citrus aurantifolia* (Christm.) Swingle
7	บ๊วย	*Prunus mume*
8	กานพลู	*Syzygium aromaticum*
9	สมอไทย	*Terminalia chebula* Retz.
10	อบเชยญวณ	*Cinnamomum loureiroi*
11	หล่อฮั่งก๊วย	*Siraitia grosvenorii*
12	ผิวส้มจีน	*Citrusx sinensis*
13	ชะเอมไทย	*Albizia myriophylla* Benth
14	ขมิ้นอ้อย	*Curcuma zedoaria*
15	กะเพราแดง	*Ociemum tenuiflorum* L.
16	มะแว้งเครือ	*Solanum trilobatum* L.
17	เทียนขาว	*Cuminum cyminum* L.
18	ผักชีลา	*Anethum graveolens* L.
19	ใบสวาด	*Caesalpinia bonduc*
20	ตานหม่อน	*Vernonia elliptica* DC
21	มะแว้งต้น	*Solanum indicum* L.
22	โกฐจุฬาลัมพา	*Artemisia annua* L.
23	น้ำผึ้ง	*Apis mellifera* L.
24	ดีปลี	*Piper longum*
25	ขิง	*Zingiber officinale*
26	พริกไทยล่อน	*Piper nigrum* L.
27	ว่านน้ำ	*Acorus calamus*
28	พิมเสน	*Pogostemon cablin*
29	เก๊กฮวย	*Chrysanthemum morifolium* Ramat.
30	เสนียด	*Justicia adhatoda*

BIOGRAPHY

NAME	Ladda HER
DATE OF BIRTH	14/02/1990
PLACE OF BIRTH	Vientiane Capital city, Lao PDR
ADDRESS	House namber 003, Unit 02, Nalao Village, Sikottabong District, Vientiane Capital, Lao PDR
POSITION	Assistant Lecturer at Faculty of Pharmacy, University of Health Sciences, Vientiane, Lao PDR
PLACE OF WORK	Department of Pharmaceutical Care, Faculty of Pharmacy, University of Health Sciences, Samsenthai Rd, Kaoyord Village, Sisattanak District, Vientiane, Lao PDR, Zip code 7444, Fax: +85621217865
EDUCATION	2011 Bachelor's degree of Pharmacy, Faculty of Pharmacy, University of Health Sciences, Lao PDR 2021 Master degree in Clinical Pharmacy, Faculty of Pharmacy, Mahasarakham University, Thailand
Research grants & awards	Thesis support fund for graduate students, Faculty of Pharmacy, year 2018