


# Natural products for chronic cough: Text mining the East Asian historical literature for future therapeutics

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## Abstract

Chronic cough is a significant health burden. Patients experience variable benefits from over the counter and prescribed products, but there is an unmet need to provide more effective treatments. Natural products have been used to treat cough and some plant compounds such as pseudoephedrine from ephedra and codeine from opium poppy have been developed into drugs. Text mining historical literature may offer new insight for future therapeutic development. We identified natural products used in the East Asian historical literature to treat chronic cough. Evaluation of the historical literature revealed 331 natural products used to treat chronic cough. Products included plants, minerals and animal substances. These natural products were found in 75 different books published between AD 363 and 1911. Of the 331 products, the 10 most frequently and continually used products were examined, taking into consideration findings from contemporary experimental studies. The natural products identified are promising and offer new directions in therapeutic development for treating chronic cough.

## Keywords

Chronic cough, text mining, historical literature, natural products, herbs, plants

## Introduction

Cough significantly impacts patients and is the most common reason for visits to general medical practitioners.<sup>1</sup> Chronic cough can be caused by a variety of disorders including cancer, chronic obstructive pulmonary disease (COPD), tuberculosis, smoking, the use of angiotensin-converting enzyme inhibitors, rhinosinus conditions, asthma, gastroesophageal reflux disease or combinations of these.<sup>2</sup> Cough may persist following respiratory infections, be induced by seasonal allergens or environmental pollutants and in a small percentage of patients the cause cannot be diagnosed.<sup>3</sup> The cough reflex occurs when mechanical changes, irritants or inflammatory changes stimulate afferent or sensory nerves in the larynx and tracheo-bronchial tree. In some people, the cough reflex can become sensitized and lead to chronic cough.<sup>4</sup>

Clinicians and researchers are continually looking for new interventions, and there is a need for broadened and improved treatment options that have an

acceptable risk–benefit ratio.<sup>5</sup> In the search for new treatments, medicinal plants may provide insights and directions for therapeutic development. Text mining historical literature, such as the classical Chinese medicine literature, provides a rich and voluminous source of information that dates back to approximately BC 200. This literature includes historical references to

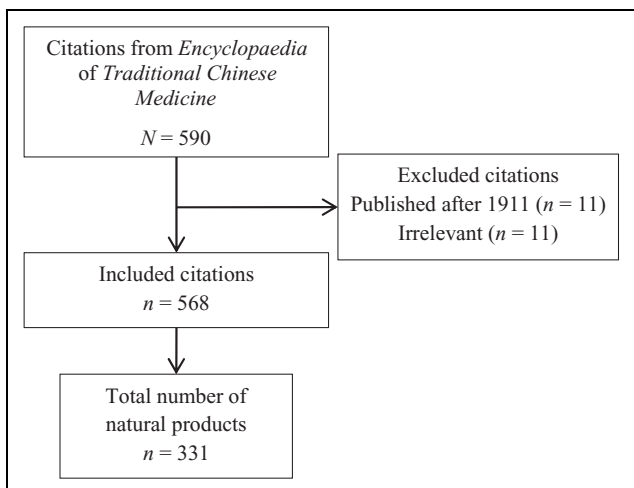
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**Figure 1.** Flow diagram of included citation.

plants and other natural products for a wide range of health conditions and still informs contemporary herbal medicine clinical practice.<sup>6</sup>

A number of drugs have originated from natural products used in traditional medicines.<sup>7,8</sup> A recent review reported that from 122 drugs derived from natural sources, 80% were developed for the same indication as their traditional use.<sup>6</sup> Some well-known drugs used for cough are derived from plant compounds, such as codeine from opium poppy (*Papaver somniferum*) and pseudoephedrine from *Ephedra sinica*.<sup>5,9</sup> However, safer and more effective treatments are still needed, and it is possible that other natural products could be developed into drugs.

Researchers have proposed that screening the historical literature can be a targeted approach in identifying plants for further investigation of novel pharmacological agents.<sup>6,10,11</sup> In the last 5 years, researchers at RMIT University (Australia) have developed text mining methods and conducted comprehensive analyses of the classical Chinese medicine literature approach for conditions such as dementia.<sup>12</sup> The detailed methodology has been published elsewhere.<sup>13</sup> This study used a similar approach to identify plants used in the historical literature for chronic cough. The approach aimed to identify prospects for future clinical and experimental studies, which may lead to the development of new treatments for chronic cough.

## Methods

The following Chinese terms for chronic/long-term cough were used to search the literature: ‘*jiu ke* (久咳)’, ‘*jiu sou* (久嗽)’, and ‘*jiu ke sou* (久咳嗽)’.

These terms were checked against dictionaries and medical nomenclatures to ensure historical terminology was accurate for the time periods covered in the search.<sup>14–16</sup>

We searched the *Encyclopaedia of Traditional Chinese Medicine (Zhong Hua Yi Dian, 4th edition)*. It contains over 1000 medical books and was selected because it is the most comprehensive collection available in electronic format.<sup>17</sup> The search terms were entered separately, and the results merged into one data set. The following data were extracted: plant name(s), book titles, author(s) and signs and symptoms treated. Since the focus was on the ‘historical’ or ‘classical’ literature of Chinese medicine, only citations in books written or published during the dynastic period of Chinese history were included. Each citation was assessed by an expert in respiratory medicine and historical literature to consider the likely disorder being described.

Inclusion criteria were: (1) citations that mentioned chronic cough and (2) articles that described the treatment of chronic cough with natural products, such as plants, minerals and animal substances. Citations were excluded if: (1) they described conditions that did not have chronic cough as the main symptom and (2) the citation was from a book written after the fall of the Qing Dynasty in 1911.

## Results

Search and analysis revealed 590 citations for chronic cough. Eleven citations published after 1911 were excluded. Another 11 were excluded because they included cough as an incidental symptom to postpartum conditions ( $n = 7$ ), disorders of the mouth and teeth ( $n = 2$ ), stroke ( $n = 1$ ) and worm infestation ( $n = 1$ ). After exclusions, 568 citations were evaluated (see Figure 1).

Chronic cough was mentioned in 75 different books published between AD 363 and 1911. The earliest reference was found in the *Handbook of Therapies for Emergencies (Zhou Hou Bei Ji Fang)*, compiled by the official *Ge Hong* in AD 363. In this book, three different plant combinations and syrups were used to treat chronic cough. The book, *Prescriptions for Universal Relief (Pu Ji Fang (1406))* contained the most references ( $n = 171$ , 30%). Most citations ( $n = 306$ , 54%) were published in the period between 1368 and 1644 (Ming Dynasty). This result is not surprising because during the 14th to 17th centuries, medical book publishing increased and the number of natural products

**Table 1.** Frequently used herbs to treat chronic cough from historical literature.

Number	Scientific name, authority and family	Common name	Frequency	Current use <sup>20</sup>
1	<i>Zingiber officinale</i> (Willd.) Rosc., Zingiberaceae	Ginger root	212	All types of cough, phlegm
2	Honey	Honey	174	All types of cough, dry cough
3	<i>Glycyrrhiza uralensis</i> Fisch., Fabaceae	Licorice root	169	All types of cough
4	<i>Prunus armeniaca</i> L., Rosaceae	Apricot kernel	166	All types of cough, dry cough
5	<i>Tussilago farfara</i> L., Asteraceae	Coltsfoot flower	139	All types of cough
6	<i>Panax ginseng</i> C.A. Mey., Araliaceae	Ginseng root	120	Dry cough
7	<i>Aster tataricus</i> L.f., Asteraceae	Aster root	109	All types of cough
8	<i>Morus alba</i> L., Moraceae	Mulberry root bark	101	All types of cough
9	<i>Schisandra chinensis</i> (Turcz.) Baill., Magnoliaceae	Schisandra fruit	99	Dry cough
10	<i>Fritillaria cirrhosa</i> D. Don., Liliaceae	Fritillaria bulb	88	Dry cough
11	<i>Citrus tangerina</i> Hort.et Tanaka., Rutaceae	Tangerine peel	81	Productive cough with phlegm
12	<i>Pinellia ternata</i> (Thunb.) Breit, Araceae	Pinellia rhizome	73	Productive cough with phlegm
13	<i>Platycodon grandiflorum</i> (Jacq.) A.DC., Campanulaceae	Platycodon root	68	All types of cough, phlegm
14	<i>Poria cocos</i> (Schw.) Wolf., Polyporaceae	Poria	66	Productive cough with phlegm
15	<i>Equus asinus</i> L., Equidae	Gelatin	66	Dry cough
16	<i>Cinnamomum cassia</i> Presl., Lauraceae	Cinnamon bark/twigs	62	Cough and wheezing
17	<i>Asarum heterotropoides</i> F.Schm. var. <i>mandshuricum</i> (Maxim) Kitag., Aristolochiaceae	Chinese wild ginger root	51	Productive cough with phlegm
18	<i>Ziziphus jujuba</i> Mill. Var. <i>inermis</i> (Bge.) Rehd., Rhamnaceae	Red date	50	Long term weak cough
19	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch., Scrophulariaceae	Rehmannia root	48	Long term weak cough
20	<i>Ephedra sinica</i> Stapf., Ephedraceae	Ephedra aerial parts	47	Cough and wheezing

listed in materia medica books rose to a peak of 1892.<sup>18,19</sup>

### Types of chronic cough

A range of different types of chronic cough were identified including cough with phlegm (81 citations) and dry cough (5 citations). In 17 citations, a bronchitis-type cough was described with symptoms of cough for several years accompanied by dyspnoea. Tuberculosis was the potential cause of cough in 30 citations, which included symptoms of haemoptysis, fever and/or terms for tuberculosis (*fei lao* 肺癆, *lao bing* 癆病). Eleven citations appeared to be similar to asthma and described wheezing as well as mentioned the Chinese terms for asthma (*xiao chuan* 哮喘, *xiao* 哮).

### Natural products for chronic cough

The 568 citations mentioned 331 distinct natural products including plants ( $n = 250$ ), animal substances ( $n = 47$ ) and minerals ( $n = 34$ ). Most citations

used natural product combinations to treat chronic cough ( $n = 518$ ) and a small number used single products ( $n = 50$ ). The top 20 commonly used natural products were identified based on frequency (see Table 1). From this group, 10 had 88 or more individual references and were considered to be the 'most frequently used'. The three most common natural products were ginger root (*Zingiber officinale*), honey and licorice root (*Glycyrrhiza uralensis*). Ginger and mulberry root bark were commonly used for productive cough, whilst honey and fritillaria bulb were the most frequently used for dry cough. Ephedra and opium poppy were both cited for chronic cough but at lower frequencies.

### Discussion

It cannot be determined whether the citations of chronic cough found in the Chinese classical literature referred to conditions that would present in contemporary clinical practice but the natural products for

chronic cough are strikingly similar to those used in contemporary Chinese medicine.

The current understanding of chronic cough, that is, lasting 8 weeks or more, is due to an enhanced sensitivity of cough receptors in the airways that transmit signals to the cough centre in the brain stem via the vagus nerve. Although a reflex, cough is mediated by higher cortical centres, and changes in central processing may also be associated with enhanced cough response.<sup>3</sup> Chronic cough in the absence of notable airway pathology or identifiable irritants may be due to airway inflammation and remodelling and/or increased neuronal activation, akin to allodynia, which may be a consequence of viral antigens or other pro-inflammatory factors,<sup>21</sup> and research on the effects of amitriptyline and gabapentin support the involvement of neuropathic mechanisms in chronic cough.<sup>22</sup>

### Actions of the most frequent natural products

The 10 most frequently cited products are still used to treat cough in clinical practice in China.<sup>20</sup> Each has been investigated in experimental studies.

Ginger root is used to relieve coughs and colds and has similar uses in other systems of traditional medicine.<sup>23,24</sup> It has been reported to exert antimicrobial and anti-inflammatory actions.<sup>25</sup> In a mouse model of asthma, an extract of ginger combined with another of the plants in the top 20, *Pinellia ternata*, was found to inhibit airway inflammation and mucus hypersecretion.<sup>26</sup>

In a human respiratory tract cell line, a water extract of ginger dose dependently inhibited human respiratory syncytial virus.<sup>27</sup> Ginger has been used to treat pain in clinical trials.<sup>28</sup> In animal models, ginger extracts have been found to possess analgesic and anti-inflammatory properties<sup>29</sup> and potentiate morphine-induced analgesia.<sup>30</sup>

Honey has also been used in other traditions in cough syrups<sup>31</sup> and a recent Cochrane review of clinical studies reported that honey was effective in reducing cough frequency in children.<sup>32,33</sup> A meta-analysis of clinical studies reported that the post-operative administration of honey following tonsillectomy reduced pain and promoted wound healing<sup>34</sup> and has been found to reduce pain in aphthous ulcers.<sup>35</sup> In animal models of pain and inflammation, honey reduced pain perception, especially in inflammatory pain.<sup>36</sup>

Licorice root is used in multiple medical traditions and contains a large number of biologically active

constituents known to have anti-inflammatory, antiviral, antimicrobial, antioxidative, immunomodulatory and other activities.<sup>37</sup> In humans, licorice has been reported to reduce post-operative sore throat and cough induced by intubation.<sup>38,39</sup> In guinea pigs, extracts of licorice were found to reduce capsaicin-induced cough and the effect persisted 4 hours after administration. The most potent antitussive compound was identified as liquiritin apioside, which appears to act peripherally in the airway and also centrally via serotonergic systems.<sup>40</sup> In guinea pigs, the oral administration of an aqueous extract of licorice reduced citric acid-induced cough and the effect was more pronounced than in codeine controls.<sup>41</sup> In an asthma model using ovalbumin-sensitized mice, glycyrrhizic acid significantly attenuated airway resistance and suppressed the generation of a Th2-type immune response.<sup>42</sup> Licorice has been reported to contain compounds that possess analgesic and antispasmodic actions<sup>43</sup> and in guinea pig tracheal smooth muscle cells, its flavonoid isoliquiritigenin produced concentration-dependent relaxation.<sup>44</sup> The combination of licorice and *Paeonia lactiflora* root has a long history of use in pain and a recent study showed dose-dependent and time-dependent anti-allodynic and anti-hyperalgesic effects for this combination in a rat model of neuropathic pain.<sup>45</sup>

The fourth most commonly cited was *Prunus armeniaca*. Its kernel, commonly known as apricot seed, contains several active compounds such as the glycoside amygdalin, amygdalase and arachidic acid.<sup>46,47</sup> Mice stimulated with methotrexate and then treated with *P. armeniaca* showed reduced toxic effects and reduced oxidative stress.<sup>48</sup> In rats, injection of amygdalin reduced nociceptive behaviours.<sup>49</sup> An oil derived from *P. armeniaca* kernel has shown activity against a number of gram-positive and gram-negative bacteria and yeasts.<sup>50,51</sup> However, the therapeutic applications of apricot seed may be limited by reported toxicity and the presence of cyanogenic glycosides.<sup>52</sup>

*Tussilago farfara* (Coltsfoot), which was the fifth most frequent plant, has been used extensively in Europe and other countries for its antitussive and expectorant properties.<sup>53</sup> Its botanical name is derived from the Latin *tussis*, meaning 'cough'. Coltsfoot extracts have also been reported to possess antioxidant properties.<sup>54</sup> In Europe, the leaves are often used, whereas in China it is the flower that is used for cough.<sup>20,55</sup> In Europe, toxicity issues have led to its therapeutic use being restricted to varieties with low pyrrolizidine alkaloid content.<sup>56</sup>

Ginseng root is not generally classed as a medicine for cough, but it is frequently used in formulae for chronic cough. Ginseng has anti-inflammatory and antioxidant effects<sup>57</sup> and has been reported to increase survival rate in human lung epithelial cells infected with influenza A.<sup>58</sup> An extract has been reported to exert analgesic and anti-inflammatory actions in mice,<sup>59</sup> and both its glycoprotein and saponin fractions have been reported to have antinociceptive activity.<sup>60,61</sup> Ginseng is being studied in clinical trials for its effects on coughing, shortness of breath, lung function and quality of life in COPD patients.<sup>62,63</sup>

Schisandra fruit has similar pharmacological properties to ginseng and both are listed in materia medica for dry cough.<sup>20</sup> Schisandra is used for a wide variety of disorders in East Asia and Russia and is regarded as having immunomodulatory effects.<sup>20,64</sup> Constituents including schisandrin and gomisin have been reported to reduce inflammation and oxidative stress in lipopolysaccharide-stimulated macrophages.<sup>65–67</sup> Extracts of schisandra have shown analgesic action in animal models,<sup>68</sup> and a model of visceral hypersensitivity showed an increase in pain threshold that appears to be mediated via serotonin.<sup>69</sup>

Aster root and mulberry root bark are reported in materia medica to possess antitussive effects and were frequently cited in the historical literature.<sup>20</sup> In an ovalbumin-sensitized mouse model of asthma, mulberry root bark inhibited airway hyper-responsiveness and airway inflammation.<sup>70</sup> Mulberry root bark has also been reported to exert anti-inflammatory and anticancer activities.<sup>71</sup> Compounds derived from *Aster tataricus* root have been shown to have antioxidant,<sup>72</sup> anticancer<sup>73</sup> and expectorant effects.<sup>74</sup> An extract of the related species *Aster yomena*, which is also used for cough, reduced airway hyper-responsiveness in ovalbumin-sensitized mice.<sup>75</sup>

Fritillaria bulb appeared in most citations for dry cough. It is reported to have smooth muscle relaxant effects.<sup>47</sup> In ammonia-induced cough in mice, four of its constituent alkaloids inhibited cough frequency, and imperiline showed dose-dependent antitussive activities as well as anti-inflammatory effects.<sup>76,77</sup> Another alkaloid, verticinone, has shown analgesic actions in animal models of inflammatory and neuropathic pain.<sup>78</sup>

Clinically, dry cough is the most common type among chronic cough patients, it is difficult to control and treat and significantly impacts on quality of life.<sup>5</sup> Of the most frequently cited plants, fritillaria, honey, ginseng and schisandra fruit are all used to

treat chronic dry cough.<sup>20</sup> Each of these has shown anti-inflammatory and antinociceptive properties in experimental studies. With regard to the 10 natural products frequently used for chronic cough, most have been reported to exert anti-inflammatory and/or antinociceptive effects and half had antibacterial and/or antiviral actions. However, there was considerable variation in the availability of published research with licorice having received considerable attention compared to few studies for aster root. In addition, research using animal models of cough was infrequent, so further research is needed to assess the antitussive effects of these natural products and their constituents and to investigate how these modulate pathophysiological pathways associated with cough.

## Conclusions

Evaluation of the historical literature from East Asia provides one method for identifying natural products that can be further investigated for their effects on chronic cough. This approach has become more feasible in the last few years due the advent of digital collections and systematic methods for mining the literature. The results from this study indicated that the natural products currently used in traditional medicines have substantial histories of use for chronic cough and a number of these products receiving clinical and experimental research attention for conditions where cough is a major symptom, such as COPD and asthma.<sup>62,79</sup>

Each of the 10 natural products reviewed in this article have shown activities that could account for its traditional use for chronic cough, with most having anti-inflammatory and antinociceptive effects. This approach to text mining may offer a targeted method for selecting natural products for further clinical and experimental evaluation in the search for therapeutics for chronic cough.

## Authors' Note

JS and BM conceived and designed the study. WL, AZ, XG, CL and CX oversaw the conduct of the study and contributed to the overall design, analysis and write-up.

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## Conflict of interest

The authors declared no conflicts of interest.

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