



REVIEW

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## Natural remedies for acute post-viral cough in children

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Received 11 November 2020; Accepted 19 February 2021

Available online 1 May 2021

### KEYWORDS

glycerol;  
herbal medicines;  
honey;  
natural compounds;  
post-viral acute  
cough

### Abstract

The post-viral acute cough is the most common symptom in childhood. Consequently, the use of cough relievers is frequent. Many products for treating cough contain natural components. An ancient tradition has always established herbal medicine and honey as effective and safe means to relieve cough. Nevertheless, very few studies adequately investigated the real effectiveness and safety of natural products in treating acute cough. There is some evidence, provided by pediatric randomized controlled trials, about honey, one multicomponent product (containing *Plantagolanceolata*, *Grindelia robusta*, *Helichrysum italicum*, and honey), and *Pelargonium sidoides*. Other group of substances, including glycerol and isolated natural compounds, can help manage cough but robust evidence still lacks in children. There is an urgent need to perform rigorous studies that confirm the natural products' efficacy and safety for relieving post-viral acute cough.

**Key points:** Acute post-viral cough is prevalent in childhood and adolescence. There is a growing interest concerning the use of natural remedies for post-viral cough. Many herbal medicines could be used satisfactorily for this issue.

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<https://doi.org/10.15586/aei.v49i3.71>

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## Introduction

Cough is a symptom associated with a protective reflex from the airways.<sup>1</sup> Acute cough lasts for less than 4 weeks and is caused by the upper respiratory tract infection (URTI) in most cases.<sup>2</sup> Consistent, acute cough because of URTI is the most common reason to seek medical attention in primary care.<sup>3</sup> URTI is usually of viral origin, so the term used currently is post-viral acute cough. It is generally self-resolving, but could be very annoying for the child as well as the family.

Consequently, many parents acquire non-prescription, over-the-counter (OTC) cough remedies for their children.<sup>4</sup> Likewise, many primary care doctors prescribe these products as first-line of treatment.<sup>5</sup> Concerning these non-pharmacological remedies for cough, in 2020, the Italian market revealed a sales volume of M€55 for medical devices and M€150 for food supplements.

Oral OTC remedies for cough have different compositions and actions.<sup>6-13</sup> These may be classified into various groups, such as (i) synthetic molecules with a

pharmacological mechanism of action, (ii) complex natural products, (iii) natural-identical compounds, and (iv) natural-derived isolated compounds, as reported in Table 1.

There is little evidence whether the OTC products containing pharmacological molecules are beneficial, as documented by a recent meta-analysis.<sup>14</sup> Moreover, some OTC drugs presented severe concerns about safety, including fatalities, primarily in accidental overdosing. As a result, the regulatory agencies withdrew some OTC medicines containing mucolytics and expectorant drugs for babies aged less than 2 years,<sup>15-17</sup> antihistamines and antitussives for children aged less than 6 years,<sup>16,17</sup> and decongestants meant for children aged less than 12 years.<sup>16,17</sup>

A recent review has described and discussed various OTC synthetic molecules used to relieve acute post-viral cough.<sup>18</sup> Therefore, the current review is solely concerned with natural remedies.

The use of non-pharmacological therapies is growing with the mindfulness that these compounds, mostly natural, are useful and overall safe. In addition, the literature is sparse with studies investigating natural remedies for

**Table 1** Different categories of products for the treatment of post-viral acute cough and their mechanism of action.

Category	Pharmacological products	Natural products: Extracts from medicinal plants or complex natural substances	Nature-identical compounds The substances in this group are obtained by chemical synthesis and are chemically identical to a substance naturally present in the material of vegetable or animal origin Glycerol (solely or as syrup ingredient)	Nature-derived isolated compounds. Chemical processes isolate the substances in this group from a material of vegetable or animal origin, and they are chemically identical to a substance naturally present in nature Glycerol, menthol, thymol, etc.
Types	Antitussives (central or peripheral) Expectorants Mucolytics Antihistamine-decongestant combinations Antihistamines Fixed combination with different pharmacological agents	Honey as a food; honey blended with complex extracts of herbal medicines; complex extracts of herbal medicines (usually as a blend).		
Mechanism of action	An interaction between the molecules of the substance in question and a cellular constituent is usually referred to as a receptor, which either results in direct response or blocks the response to another agent.	Complex mixture of substances with concerted activities. Complex interactions with the human body bring changes to physiological functions that cannot be pinpointed at the single target/receptor level.	Their action mechanisms are different from that of an identical substance in the contest of a complex natural matrix; they may contain residues from the chemical process. They predominantly act in targeted interaction between a molecule and its specific receptor or targeted effector.	Their actions are different from that of an identical substance in a complex natural matrix; they may contain residues from the chemical process. They predominantly act in targeted interaction between a molecule and its specific receptor or targeted effector.

cough. The current review is aimed to shed some light on the so-called natural products' gray areas, thereby clarifying different categories of products available in the market for relieving post-viral acute cough.

## Natural compounds to relieve post-viral acute cough

The marketable so-called “natural” products to relieve cough contain a large variety of substances that, simplifying, can be grouped in the following three different categories: (i) natural products, such as extracts from medicinal plants or other natural complex matrices (e.g., plants exudates such as incenses and myrrh from *Boswellia*, and bee products such as honey and propolis), (ii) natural-identical compounds (e.g., synthetic glycerol), and (iii) isolated naturally derived compounds (e.g., menthol, eucalyptol, glycerol, etc.). Table 1 reports a brief description of each category. However, it is mandatory to discern these different categories of substances because they act on the body with varying action mechanisms and profoundly different effects. Their efficacy and safety are not comparable and translatable from one to the other category and product.

Complex natural substances have always been a source of therapeutic products. Until recently, isolating specific molecules from natural substances was thought to be the only means to develop new treatments. The concept prompts this assumption that only one or very few medicinal plants' constituents are responsible for their activity. However, the bioactive compounds are naturally produced very rarely as isolated molecules in plants, but they usually occur in mixtures with other, potentially bioactive, secondary molecules.<sup>19</sup>

Even though many conventional drugs or precursors are derived from plants, there is a fundamental difference between administering a pure chemical and the same chemical in a plant matrix. Complex natural substances interact with multiple targets, which are interconnected and interrelated but not individually identifiable and quantifiable as separate and hierarchically organized interplays.<sup>20</sup> Although synthetic and food-derived vitamins or other substances are identical structurally, a complex natural matrix is rich in numerous nutrients and phytochemicals, which may influence its bioavailability and bioactivity.

A single herbal extract could be seen as a nature-designed multi-agent system that could simultaneously target a range of desirable therapeutic effects. We could say that for most, if not for all, herbal extracts, the “active constituent” is the whole extract itself. This explains, why so many herbal extracts have been challenging to identify the “active constituent.” Foods' and complex medicinal plants' matrices share the same chemical complexity, and their type of interactions with the body is very similar. Herbal extracts are seen as “intelligent” mixtures of substances selected by evolutionistic processes, and they interact as a “system” with the body (that is a system itself), as some authors are sustaining with a new intriguing approach.<sup>21</sup> These concepts could explain why bioactivity-guided fractionation of plant matrix frequently leads to the loss of effects; in fact, the effects could be measured only in a

complex extract, where several compounds interact to constitute bioactivity.<sup>22</sup>

A crucial issue concerning the complex natural matrices is the quality control process. Considerable differences in harvest yields and chemical composition of plant extracts could be determined by seasonal and climate factors such as temperature and humidity, contamination of soil, and harvesting conditions. There is evidence that higher antioxidant concentrations and lower cadmium (Cd) concentrations are linked to specific agronomic practices (e.g., prohibition of the use of synthetic chemical crop protection products and certain mineral fertilizers (all N, KCl and superphosphate) adopted in organic farming systems. On average, organic crops have higher concentrations of antioxidants, lower Cd concentrations,<sup>23</sup> and a lower incidence of pesticide residues than nonorganic comparators across different regions and production seasons.<sup>24</sup> Storage of plant materials and post-harvest processing, during extraction and preparation, influence phytochemical contents and may significantly display batch-to-batch variations.<sup>22</sup>

Many products available in the market containing extracts of medicinal plants (particularly food supplements) are standardized by one single biomarker, which is easy to measure but does not assess the whole matrix's complexity. Moreover, this biomarker could be unrelated to the pharmacological action of the herbal preparation. Standardization of all relevant constituents within a plant, plant mixture, or plant-derived product could be guaranteed by “-omic” technologies (genomics, transcriptomics, proteomics, and metabolomics). Recently, untargeted metabolomics have been successfully applied to assess natural substances' quality, plant extracts, and corresponding formulated products. These procedures assure the batch-to-batch constancy of various active ingredients, guaranteeing consistent quality and clinical efficacy.<sup>25</sup> Moreover, a product's natural integrity could be challenged by artificial preservatives, colorants, and excipients.

Recent developments in molecular biology could also pave the way to understand complex plant mixtures' multifaceted activities. The complexity of natural substances could be seen as a resource and not necessarily a limit. This complexity could be fruitful in treating cough. New pathogenic mechanisms in acute cough, including the urge to cough sensation, have been identified recently. The cortical neural network, pharyngeal sensory innervation, airway mechanical stimulation, inflammatory mediators, and postnasal drip participate actively in the onset and maintenance of acute cough and the urge to cough phenomenon.<sup>26</sup> It has been demonstrated that the application of mechanical stimuli in the form of air puffs to the lateral posterior oropharyngeal walls elicits a cough response preceded by the urge to cough.<sup>27</sup>

Consequently, it has been postulated that two mechanisms could elicit cough: the repetitive mechanical stimulation of the lateral posterior oropharynx wall, and the pharyngeal irritation secondary to drying and evaporative cooling of the mucosa. This type of cough includes a motivational component (sensing the urge to cough) and may be essential to maintain adequate protection of airways.<sup>27</sup> Suppose the pharynx has such a crucial role in determining the urge to cough. In this case, it is consequent that medicinal plants and complex natural substances with

protective, emollient, and lubricating effects on the pharynx have been taken for millennia to relieve cough.

## Natural products

Traditional western medicine includes numerous popular remedies to treat URTI. The natural extracts are blended in specific mixtures, which are contained in products available as medical devices, food supplements, or herbal medicines. The rationale for their use is frequently based on *ex vivo* experiments, *in vitro* evidence, or only on empirical knowledge. However, some recent randomized controlled trials (RCTs) have provided evidence that some products are effective and safe in relieving post-viral acute cough.

Medicinal plants, traditionally used as a remedy for cough, contain numerous phytochemicals that can allay cough directly or indirectly. In post-viral acute cough, one of the primary objectives is to resolve pharynx irritation and inflammation and to help patients control the “urge to cough,” such as the need to cough. According to a recent survey, 98% of people suffering from a common cold perceived this sensation; two-thirds of these patients declared unable to control the impellent need of coughing and considered troublesome both the urge to cough and the coughing.<sup>28</sup> Medicinal plants, exerting a protective and demulcent effect on the pharyngeal mucosa, are rich in particular classes of substances, including polysaccharides (particularly mucilage), resins, saponins, essential oils, and polyphenols.

**Mucilage polysaccharides.** These are large, highly branched polymeric structures built from different sugars and uronic acid units. Mucilage polysaccharides, used in children with acute cough, are contained in marshmallow (*Althaea officinalis*), mallow (*Malva sylvestris*), ribwort plantain (*Plantago lanceolata*), and Iceland moss (*Cetraria islandica*).

Mucilage polysaccharides are primarily used for their topical emollient and internal demulcent properties. Thanks to their bioadhesive-mucoadhesive properties and high hydrophilic nature, they can trap water and other molecules, forming a gel.<sup>29</sup> These properties led to the formation of a polysaccharide layer on the upper airway mucosa. The mucosal bioadhesive and muco-protective activities exerted by polysaccharides are utilized in oral and gastric disorders.<sup>30–34</sup> An experimental *in vivo* study demonstrated that polysaccharide fractions extracted from various medicinal plants could effectively and significantly reduce cough.<sup>35</sup> The mucosal arabinogalactan-polysaccharide layer could indirectly influence cough receptors’ sensitivity to suppress cough.

**Natural resins.** These are sticky, water insoluble substances produced naturally by different plants as a healing or self-defense mechanism. Important resin-containing herbs include gumweed (*Grindelia robusta*), myrrh (*Commiphora myrrha*), various balsams, and propolis, which is a complex resinous substance collected by bees from resinous plants.

When damaged by natural or artificial incision, plants produce resins secreting a viscous fluid that soon hardens. The protective activities of resins on mucosae are well known.<sup>36</sup>

**Saponins.** These are a class of natural compounds found abundantly in more than 100 families of plants that possess surfactant properties. Saponins-containing herbs used traditionally to treat cough in children are gumweed (*Grindelia robusta*), English ivy (*Hedera helix*), and cowslip (*Primula veris*).

In an aqueous solution, saponin molecules align themselves vertically on the surface with their hydrophobic ends oriented away from the water. Saponins reduce the surface tension of water. In traditional medicine, saponins have always been considered expectorants for their mucus-thinning properties. One of the hypothesized mechanisms of action is that saponins, coming in contact with the mucus, make it less sticky and more comfortable to be discharged.<sup>37</sup> Owing to their polar nature, saponins are sparingly absorbed from the gastrointestinal tract, so they usually do not produce systemic effects when administered orally.<sup>38</sup>

**Polyphenols.** These are natural compounds synthesized exclusively by plants; they possess chemical features related to phenolic substances and elicit strong antioxidant properties. There is a wide range of compounds: for example, flavanols, anthocyanidins, anthocyanins, iso-flavones, flavones, flavonols, flavanones, and flavanonols. These substances are present in medicinal plants, complex substances such as honey and propolis, and generally in all vegetables and fruits. Flavonoids, anthocyanidins, and many other phenolic compounds have antioxidant, anti-inflammatory, antibacterial, and immunomodulant effects. These activities are useful to cure URTI.<sup>11</sup>

**Essences.** They contribute to the flavor and fragrance of plants. Essential oils happen from the distillation of aromatic plants. Plants rich in essential oils commonly used to improve cough are thyme (*Thymus vulgaris*), eucalyptus (*Eucalyptus globulus*), mint (*Mentha piperita*), fennel (*Foeniculum vulgare*), and tea tree essential oil (*Melaleuca alternifolia*).

Essential oils are volatile, lipophilic, insoluble, and immiscible in water. Essential oils are complex mixtures of many biologically active constituents.<sup>39</sup> These are administered through inhalation (e.g., eucalyptus oil), orally (e.g., peppermint oil), and transdermally (e.g., tea tree oil).

## Complex natural substances in treating post-viral cough with evidence of efficacy provided by randomized clinical trials in children

### Honey as a food

Honey is a natural substance with a complex composition where carbohydrates are the main constituents accounting for about 95% of the dry matter. Honey contains flavonoids that originate from nectar, pollen, and plant resins collected by bees. Such flavonoids indicate the botanical and geographical origins of honey and have associated health benefits.<sup>40</sup>

Honey contains other phytochemicals such as resin obtained when a bee sucks the nectar of flowers or

secretions from plants' living parts. The primary polyphenol compounds in honey are flavonoids and phenolic acid, responsible for inhibiting oxidation because of their ability to reduce the free radical formation and scavenge free radicals.<sup>41</sup>

Honey always has been considered a traditional remedy for cough.<sup>42,43</sup> The World Health Organization (WHO) believes honey to be a cheap, accessible, and safe demulcent to relieve URTI-associated cough in children.<sup>44</sup> Honey has anti-inflammatory, antioxidant, antibacterial, and metabolic activities.<sup>45</sup> The effect of honey on cough is the expression of multiple effects of its numerous components. Flavonoids and phenolic acids concur with their antioxidant effect, and sugars and resins confer sweetness and viscosity. Viscous substances provide a more prolonged sweet taste than sugared water as they tend to stick to the oral mucosa and teeth. The sweet taste can send pleasant stimuli to the cerebral cortex, superseding the viral inflammation's irritative sensations, and viscosity increases production of saliva and swallowing. It limits the transmission of irritative stimuli to the cortical neural network and interferes with the urge to cough.

There is evidence that honey is useful for symptomatic relief of nocturnal URTI-associated cough in reducing duration and severity of cough, in improving quality of sleep for both children and their parents.<sup>46-48</sup> Based on the result of a randomized, double-blinded study, there is no difference in efficacy between various types of honey. Indeed, in one study, where three diverse honey samples were evaluated (eucalyptus, Labiatae, and citrus honey), no significant differences were found among them.<sup>48</sup> Nevertheless, each group of children taking honey had a response better than the group of children taking the date's extract, the sweet substance used as a comparator. These results reduce the purported importance that sweet taste could have in relieving cough. The significant difference in efficacy between the honey products and the sweet silan date extract suggests that other components (e.g., flavonoids) and properties (e.g., viscosity) could contribute to honey's beneficial effects on cough.

In particular, honey could be useful in reducing the reflex of urge to cough as proposed recently.<sup>49</sup> A systematic review demonstrated that honey might offer more relief for cough symptoms in children aged more than 1 year compared to no treatment or using diphenhydramine. Still, its efficacy was not better than that of dextromethorphan.<sup>50</sup> However, it has to be underlined that administration of honey is not recommended in children younger than 1 year for infantile botulism.<sup>51,52</sup>

Manuka honey derived from the flowers of *Leptospermum scoparium*, an indigenous plant of New Zealand and Australia, exerts important bactericidal and anti-inflammatory activity, as demonstrated by an RCT.<sup>53</sup>

### **Medical devices composed of complex natural substances**

A new category of cough remedies is represented by complex natural substances found in medical devices (according to EU Directive 93/42/EC). Different from food supplements and herbal medicines, medical devices composed of these

substances exert their primary effects with physiological and non-pharmacological mechanisms. The complex natural substances represent an innovative approach to manage cough. They do not suppress cough by interacting with specific receptors, but act by protecting the oropharynx with a film that provides a local physical (mucoadhesive) barrier to pathogenic mechanisms, including postnasal drip and local inflammation caused by exogenous and endogenous substances. They also exert antioxidant and demulcent effects. This non-pharmacological mechanism of action supports this class of products as medical devices. The therapeutic effect has to be ascribed to their multicomponent characteristics. Remarkably, each of the components and the entire complex do not have a pharmacological, immunological, and metabolic mechanism of action.<sup>21</sup> In this regard, a high-quality specific polysaccharide-resin-saponins-honey-based medical device has been specifically formulated to treat post-viral acute cough. Two pediatric RCT studies have demonstrated that this medical device was more effective than placebo and carbocystein in relieving nocturnal and diurnal cough and improving all clinical scores.

In the first study, a specific combination of polysaccharides, resins, saponins, flavonoids, and honey was superior to placebo in treating nocturnal post-viral cough persisting for more than seven days.<sup>54</sup> This study was confirmed by another randomized, single-blinded, multicenter study.<sup>55</sup> This second trial included 150 children with acute cough because of URTI; patients were treated with the polysaccharide-resin-saponins-honey-based medical device, or carbocysteine, for four consecutive days. The medical device induced a more rapid and significant improvement in all measured parameters, such as nocturnal and daytime cough and quality of sleep in both children and parents. Children receiving this natural product established no or minimal risk of adverse effects such as abdominal pain, nausea, and vomiting, which were common unspecific side effects recorded in placebo groups. In particular, the efficacy of honey could be potentiated by the plant extracts of *Grindelia robusta*, *Plantago lanceolata*, and *Helichrysum italicum*, which exert protective, demulcent, anti-inflammatory, and adjunctive cytoprotective effects.

## **Single complex extracts of herbal medicines with evidence in the treatment of a post-viral cough in children**

### **Plants rich in polysaccharides**

#### ***Althaea officinalis* L. (Marshmallow)**

The *Althaea* root contains mucilage polysaccharides; they consist of a mixture of galacturonorhammans, arabinans, glucans, and arabinogalactans. Marshmallow is "generally recognized as safe" in amounts usually found in foods by the US Food and Drug Administration (FDA).<sup>56</sup>

*Althaea* polysaccharides have moderate bioadhesive properties. The consolidated use of aqueous extracts of polysaccharides rich plants for cough is related to the polysaccharides' bioadhesive properties on the epithelial mucosa, leading to the formation of a polysaccharides layer on the mucosa of upper airways.<sup>35</sup> Monographs of the European Scientific Cooperative on Phytotherapy (ESCOP),



the most authoritative source of scientific evidence on phytotherapy, have stated that the mucilage from marsh-mallow root and mallow flower covers the mucosa, especially of the mouth and pharynx, protecting them from local irritation.<sup>33</sup> Hence, ESCOP therapeutic indications for *Althaea* extracts are dry cough and irritation of the oral and pharyngeal mucosa. However, no RCT study has confirmed the efficacy of *Althaea* single extract for post-viral acute cough in children.

#### *Cetraria islandica* L. (Iceland moss)

The main constituents are polysaccharides (more than 50%), mostly lichenans, and bitter-tasting lichen acids. Anti-inflammatory and antioxidant effects have been demonstrated for *Cetraria islandica* extracts.<sup>57</sup> The substance has a demulcent effect because of the polysaccharides content.<sup>58</sup> The ESCOP indications for *Cetraria islandica* are dry cough and irritation/inflammation of the oral and pharyngeal mucosa.<sup>59</sup> No RCT study has confirmed the efficacy of *Cetraria islandica* as a single extract for post-viral acute cough in children.

#### *Malva sylvestris* L. (High mallow)

Mallow flowers contain mucilage (6-8% as galacturonorhammans and arabinogalactans), flavonoids, anthocyanins, and tannins. Mucilage is one of the major components responsible for the therapeutic effects of *Malva sylvestris*, primarily due to the cough-suppressive activities.<sup>60</sup> Mucilage covers the epithelium, especially of the mouth and pharynx, affording protection from local irritation. ESCOP indications for *Malva sylvestris* are the treatment of cough, bronchitis, and inflammation of the mouth and pharynx.<sup>61</sup> Antioxidant activity of the plant has been established in different assays. No RCT study has confirmed the efficacy of *Malva sylvestris* single extract for post-viral acute cough in children.

#### *Plantago lanceolata* L. (English plantain)

*Plantago lanceolata* belongs to the *Plantaginaceae* family. The flowering aerial parts or leaves are used for therapeutic purposes. The characteristic constituents are mucilage polysaccharides (2-6% as glucomannans, arabinogalactans, and rhamnogalacturonans), flavonoids, and iridoid glycosides. It has therapeutical properties, such as anti-inflammatory, antioxidant, antifungal, immunostimulatory, and tissue regeneration. *Plantago lanceolata* is traditionally used for treating common cold and URTI, and soothing and suppressing the cough. The ESCOP therapeutical indications for *Plantago lanceolata* extracts are catarrhs of the respiratory tract and mild inflammation of the oral and pharyngeal mucosae.<sup>62</sup> The European Commission also approved its use for treating common cold and bronchitis-associated cough. No RCT study has confirmed the efficacy of *Plantago lanceolata* as a single extract for post-viral acute cough in children.

### Plants rich in saponins

#### *Grindelia robusta* Nutt (Gumweed)

It is a medicinal herb of the sunflower family that produces a certain amount of characteristically aromatic resin

that exudes naturally forming a thick layer on top of the flower's buds. It comprises different diterpenoid natural products. The main constituents are resins (in the variable amount of 5-20%), consisting of diterpenic acids, primarily grindelic acid.<sup>63,64</sup> *Grindelia robusta* exerts expectorant, antitussive, and anti-inflammatory activities. Traditionally, this plant was used by Californian indigenous populations to relieve cough. The ESCOP indications, based on human experiences and long-standing use, are productive cough and catarrh of the upper respiratory tract. No RCT study has confirmed the efficacy of *Grindelia robusta* as a single extract for post-viral acute cough in children.

#### *Hedera helix* L. (English ivy)

The leaves contain saponins (2.5-6%; hederacoside C is the main component), phytosterols, essential oil, flavonoids, and other phenolic compounds. Leaf preparations of *Hedera helix* are commonly used to treat acute inflammatory respiratory conditions, including acute bronchitis of viral origin and some chronic respiratory diseases, for example, asthma and chronic recurrent bronchitis.<sup>65</sup> No RCT study has confirmed the efficacy of *Hedera helix* as a single extract for post-viral acute cough in children.

#### *Primula veris* L. (Primrose)

The root has distinct components: triterpene saponins (3-10%), phenolic glycosides (up to 2.3%), and essential oil. *Primula veris* has an expectorant effect. An increase in the volume of bronchial secretion has been demonstrated in animal experiments.<sup>58</sup> ESCOP therapeutic indications are productive cough, catarrh of the respiratory tract, and chronic bronchitis.<sup>66</sup> No RCT study has confirmed the efficacy of *Primula veris* as a single extract for post-viral acute cough in children.

### Plants rich in essential oils

#### *Thymus vulgaris* L. (Thyme)

The leaves and flowers contain flavonoids and essential oils, including thymol, carvacrol, borneol, linalol, and pinene. The thyme extract is traditionally used to relieve cough. It has anti-inflammatory and antimicrobial activities.<sup>67-69</sup> A fixed combination of *Thymus vulgaris* with *Primula veris* root extracts and *Thymus vulgaris* with *Hedera helix* extracts have been tested in some studies in adults with acute bronchitis, demonstrating significantly beneficial activity in relieving cough.<sup>70,71</sup> The ESCOP indications are catarrh of the upper and lower respiratory tract.<sup>72</sup> No RCT study has confirmed the efficacy of *Thymus vulgaris* as a single extract for post-viral acute cough in children.

#### *Mentha piperita* L. (Peppermint)

The essential oil, leaves, flowering branch tips, fresh flowering plant, and the whole plant are used. The main components are essential oils, primarily menthol (35-45%) and menthone (15-20%), and flavonoids. The ESCOP therapeutical indications are the symptomatic treatment of cough and common cold.<sup>73</sup> Direct application of pure peppermint oil or preparations with a high concentration of oil directly on the nose or over the chest of infants and toddlers must be avoided because of the risk of laryngeal and bronchial

spasms. No RCT study has confirmed the efficacy of *Mentha piperita* as a single extract for post-viral acute cough in children.

#### *Eucalyptus globulus* Labill (*Eucalyptus*)

The leaves' main component is the essential oil (primarily 1,8-cineol at 45-75% concentration). The ESCOP therapeutic indications for the *Eucalyptus globulus* oil are the symptomatic treatment of cough and common cold. Notably, the direct application of pure *Eucalyptus globulus* oil or preparations with a high concentration of oil on the nose or over the chest of infants and toddlers must be avoided because of the risk of laryngeal and bronchial spasms.<sup>74</sup> No RCT study has confirmed the efficacy of *Mentha piperita* as a single extract for post-viral acute cough in children.

### Other plants

#### *Helichrysum italicum* (Roth.) G. Don.

*Helichrysum italicum* belongs to the *Asteraceae* family. *Helichrysum*'s main action is of antioxidant, thanks to the high contents of polyphenols, flavonoids, and coumarins. These substances protect against the Reactive Oxygen Species (ROS) free radicals.<sup>75</sup> The acetophenones, flavonoids, and phloroglucinols present in *Helichrysum italicum* have demonstrated inhibitory action in different arachidonic acid metabolism pathways and other pro-inflammatory mediators.<sup>76</sup> Therefore, it is used to treat cough. No RCT study has confirmed its efficacy as a single extract for post-viral acute cough in children.

#### *Pelargonium sidoides* DC

There is evidence that *Pelargonium sidoides* relieves cough in acute bronchitis in children.<sup>77,78</sup> *Pelargonium sidoides* belongs to the *Geraniaceae* family. It exerts anti-inflammatory activity and reduces the use of antibiotics for respiratory infections.<sup>79</sup> Moreover, *Pelargonium sidoides* has antiviral and antibacterial effects, and modulates tumor necrosis factor- $\alpha$  and release of nitric oxide. *Pelargonium* stimulates the production of interferon- $\beta$  and increases the activity of natural killer cells. The ESCOP therapeutic indications include relief from URTI symptoms, such as blocked or running nose and sore throat and cough.<sup>80</sup> Notably, no relevant side effects were reported. No RCT study has confirmed its efficacy as a single extract for post-viral acute cough in children.

### Nature-identical compounds and nature-derived isolated compounds with no evidence of efficacy in the treatment of post-viral cough in children from randomized clinical trials

#### Glycerol

Glycerol is a colorless, odorless, and viscous liquid; it is a polyalcohol found naturally in all cells as triglycerides. It occurs naturally in most of the fermentation processes.<sup>81</sup> Glycerol can be produced by various methods (from fats and oils by high-pressure splitting, by chemical synthesis,

by microbial fermentation, and as a by-product of producing biodiesel). Many methods lead to presence or formation of contaminants, which are of toxicological interest.<sup>82</sup> In the absence of specific information of marketed product, physicians and costumers cannot be sure whether the glycerol present is a nature-derived isolated compound or a result of chemical synthesis.

Currently, glycerol is primarily used as an intermediate chemical to produce various products, such as cosmetics, foods, and pharmaceuticals, for example, as a thickening or bodying agent in cough syrups. Glycerol does not have any receptorial actions. However, glycerol can contribute up to 85% of activity in cough syrups because of its purported lubrication properties, demulcent activity, and sweetness.<sup>83,84</sup> The humectant properties of glycerol depend on three hydrophilic alcoholic hydroxyl groups in its chemical structure that can attract and bind to molecules of water and, in addition, to exert a plasticizing effect by preventing mucosal dryness. Moreover, through its hydroxyl groups, glycerol demonstrates solubility characteristics similar to aliphatic alcohols, and this justifies it to be a ubiquitous and useful solvent for cough medicines, as glycerol, usually at 0.75-g/5-mL concentration, can be considered the only "active" ingredient of cough syrups.<sup>85</sup> Lastly, glycerol has lubricant and demulcent properties that make it to form a soothing film over the mucosa, decreases friction between moving surfaces, and relieves pain and inflammation. Its administration has not been associated with adverse effects, except at very high concentrations, when a dehydrating effect is apparent.<sup>86</sup>

No evidence is available about glycerol's efficacy in the pediatric population affected by acute post-viral cough. At present, RCTs are required to determine glycerol's efficacy as a cough treatment in children and infants aged 6 months and more. However, several health authorities, such as the WHO and Medicines and Healthcare products Regulatory Agency (MHRA), have promoted cough syrups containing glycerol because it is harmless and inexpensive.<sup>87</sup>

#### Menthol

Menthol is cyclic monoterpene alcohol with analgesic, antifungal, antipruritic, anti-inflammatory, antitussive, antiviral, and insecticidal activities.<sup>88</sup> It exerts antitussive effects as it agonizes the Transient Receptor Potential (TRP) receptors M8.<sup>89</sup> The sensation of freshness is perceived immediately after placing menthol in the mouth. Menthol is, therefore, commonly present in many cough relievers.<sup>90-92</sup> However, it could be toxic at high concentrations.<sup>93</sup> There are reports of severe but nonfatal toxicity in children who were intranasally instilled solutions containing menthol.<sup>93</sup>

#### Eucalyptol (1,8-cineol)

Eucalyptol is a cyclic ether and monoterpenoid, and represents 65.4-83.9% of eucalyptus essential oil. It has balsamic, anti-inflammatory, and antioxidant activities.<sup>93</sup> It is popularly used to relieve cough. It acts on TRP receptors.<sup>94</sup> Similar to menthol, eucalyptol is widely used in many cough

relieving natural products.<sup>95</sup> Essential oils high in 1,8-cineol (eucalyptol) can cause central nervous system (CNS) and breathing problems in young children; do not apply it too near to the faces of infants or children. Severe but non-fatal toxicity has been reported in children who were intranasally instilled solutions containing 1,8-cineol.<sup>96</sup>

### Thymol

Thymol is the main monoterpene phenol occurring in essential oils isolated from plants belonging to the *Lamiaceae* family, primarily *Thymus vulgaris*.<sup>97</sup> Thymol is employed for positive antioxidant, anti-inflammatory, local anesthetic, and antiseptic activities to relieve cough.<sup>98</sup>

### Discussion

Coughing is one of the most common reasons for consultation in routine pediatric practice. It can negatively affect sleep and daily activities, altering the quality of life of child and parents or caregivers. There are some easy strategies to implement for symptomatic relief of common cold/cough in children, such as adequate hydration, cool mist humidification, and saline nasal irrigation.<sup>99</sup> However, in the absence of effective antiviral treatment for URTI, parents try to find products that would have relief from cough until the illness is resolved; hence, natural products highly attract parents for this. Therefore, the market for cough relievers is growing, and people can find many so-called natural products for cough, usually specifically differentiated in pediatric or adult formulations. Overall, market size of cough remedies is estimated to reach \$1.45 billion by 2025, growing at a compound annual growth rate (CAGR) of 3.6% during 2020-2025.<sup>100</sup> In the last 10 years, a marked consumer shift toward naturally derived medicines and therapies, coupled with the growing concerns regarding conventional medicine's adverse effects, has caused the increasing use of natural remedies for cough. Moreover, doctors and health professionals require treatment options that have an acceptable risk-benefit ratio. In spite of the generalized use of food supplements, medical devices, and herbal medicinal products for relieving cough in blends of different extracts of medicinal plants with honey or without honey, or single isolated chemical components, evidence from RCT studies in children is still scarce. In this growing market of such products, some of the following gray areas could be identified: (1) absence of stringent regulations for approval of natural remedies in the form of food supplements for common cold, cough, and sore throat has led to an increasing number of products available in the market whose quality and safety have not been established completely; (2) confusion among consumers, and even physicians, about the meaning of the word "natural" when speaking about the enormous variety of products available in the market; and (3) difficulty for doctors and consumers to define the quality, efficacy, and safety of a natural product available in the market only on the basis of the information stated on the label. The market of cough relievers includes various categories of products such as food supplements, medical devices prepared

from natural substances, and herbal medicinal products that contain a great variety of components. These components can be of natural origin (natural complex matrices such as extracts of medicinal plants or plant exudates) or produced by chemical synthesis in an almost identical form of a natural analog or extracted from a plant matrix. Each of these categories of components interacts with the human body differently, and the effects generated could be profoundly diverse. Essentially, there are no guidelines, or an expert-defined list of rules, to choose correctly the natural products available in the market. Pharmacist's decision to suggest, and parents' decision to buy, is only based on personal elements of knowledge. Products have different compositions, concentrations, and quality of natural extracts. They are produced on the basis of diverse formulation strategies, and their overall quality relies on technological innovation and products based on different manufacturers' productive standards. There are considerable differences in different manufacturers' productive standards. Hence, it is mandatory to evaluate each product based on its characteristics, remembering that the results of pre-clinical or clinical studies of a product cannot be translated to another similar product, as is possible with "generic drugs." In this segment of market, each product has a unique characteristic, and regarding its quality, safety, and efficacy stand for itself." It is important to consider products with RCT studies of sound methodology that evaluate their effectiveness and safety, considering that most of the products available in the market do not have any study to confirm their safety and efficacy in children. It is also essential to check the long-standing use of complex natural substances present in the specific formulation. In this area of knowledge, where evidence of clinical efficacy from RCT studies is scarce, ESCOP monographs, reporting established safe use and results of pre-clinical and clinical studies, could be conceived as one of the most authoritative sources of reference for physicians.

In addition to these two fundamental aspects, we also propose a minimum set of indications, fully aware that they are not exhaustive. They can support doctors or other health professionals when choosing a product in the so-called "natural market" and when explaining to the parents the motivations of choice. If the intention is to treat using natural substances, it would be useful to evaluate the "true naturality," referring to the classification suggested in Table 1. Other essential elements to observe, particularly for general issues of safety, are the product compliance with European Medicines Agency (EMA) indications for ethanol content in products for children;<sup>101,102</sup> the absence of chemical preservatives, flavors, or stabilizers; and the use of organic farming methods for growing medicinal plants. A positive note is represented by the general safety of natural products tested in clinical trials and post-marketing observational studies. No serious adverse effects are usually reported in RCT studies evaluating medicinal plant extracts at commonly used dosages. No severe adverse reactions were observed in one prospective observational study directed to assess the occurrence of adverse reactions for Asteraceae-containing remedies in a general population sample of 18,830 patients (60.3% were children) receiving 42,378 prescriptions of Asteraceae.<sup>103</sup>



## Conclusions

In conclusion, there is evidence that some natural products significantly affect post-viral acute cough. This evidence is consistent with the popular tradition of using natural compounds to relieve cough. However, many commonly used medicinal plants and products available in the market with so-called natural components have not been sufficiently studied. Therefore, there is an urgent need to perform rigorous studies to confirm the traditional experience of natural products used to relieve cough.

## Competing interests

The authors declare that they have no competing interests.

## Funding

The publication was supported by the Italian Society of Pediatric Allergy and Immunology (SIAIP).

## Authors' contributions

All authors contributed to the study's conception and design. The first draft of the manuscript was written by GC and was critically revised by VM, MDF, GLM, VM, MAT, and MV. All authors read and approved the final manuscript.

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