

Non-pharmacological remedies for post-viral acute cough

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Abstract

The post-viral acute cough (PAC) is a widespread symptom, mainly in childhood and adolescence, and is usually associated with an acute upper respiratory infection, namely the common cold. The use of cough relievers is, therefore, impressive, as documented by the market data. There are many medical devices and dietary supplements for treating PAC, which contain non-pharmacological components. Ancient people used traditional herbs to treat PAC. Thus, a well-established tradition considers natural remedies as an effective and safe way to relieve PAC. The herbal agents include polyphenols, flavonoids, saponins, glucosides, and alkaloids. Also, the European Medicine Agency has recognized the value of plant extracts and other natural substances to treat PAC. Nevertheless, a few studies investigated the role of non-pharmacologic remedies for PAC. There is some evidence for honey, glycerol, *Althea officinalis*, *Drosera rotundifolia*, *Grindelia*, *Hedera helix*, *Pelargonium sidoides*, *Sambucus nigra*, *Thymus vulgaris*, hyaluronic acid, and saline solutions. However, further rigorous studies should confirm natural products' efficacy and safety to relieve PAC.

Introduction

Acute upper respiratory infections are the most frequent infectious disease and burden the society, from both a social and economic perspective. The common cold, such as acute rhinopharyngitis, is the most prevalent. The common cold symptoms usually

include cough, sneezing, rhinorrhea, nasal congestion, hypo/anosmia, hypo/ageusia, facial pressure, sore throat, headache, discomfort, myalgias, and low-grade fever [1]. Cough is a symptom mainly due to a protective reflex to clear airways from secretions overload [2]. The definition of acute cough establishes a duration of fewer than four weeks [3]. Acute cough represents the primary reason for accessing primary care doctors [4]. Acute upper respiratory infection, namely the common cold, is the most frequent cause of acute cough in children and adolescents [5]. Viruses, mainly rhinovirus, are the leading cause of common cold; accordingly, the post-viral acute cough (PAC) has come into everyday use [6]. The common cold symptoms usually last less than ten days; acute rhinosinusitis is suspected if they last longer or worsens before [7]. Instead, PAC lasts 3-4 weeks but is generally self-resolving [8]. However, PAC is incredibly annoying for children or adolescents and results in very uncomfortable parents [9].

Consequently, the use of cough-relievers is impressive among people [10]. Alike, doctors frequently prescribe cough-relievers as a first-line treatment for PAC [11]. In this regard, over-the-counter (OTC) products represent a relevant market share. OTC cough-relievers have different action mechanisms, including five drug classes, i.e., antitussive, expectorants, mucolytics, antihistamines, and decongestants [12]. Fixed drug combinations are prevalent and include different molecules, aiming to minimize cough reflex and constitutional symptoms. In this regard, many products contain mainly acetaminophen, ibuprofen, or other non-steroidal anti-inflammatory drugs, first-generation antihistamines, mucolytics, and expectorants. However, a recent meta-analysis reviewed the OTC medications for acute cough [13]. The analysis reported that many studies were poorly conducted, with methodological bias, and very different. Thus, there was no good evidence for or against OTC medicines' effectiveness in acute cough. Meanwhile, the regulatory agency withdrew some antitussive drugs because of safety concerns for severe adverse events, including fatalities.

On the other hand, self-care is a growing market worldwide driven by increasing consumer interest in improving their health and well-being. Consequently, there is an increasing interest in non-pharmacological remedies for PAC. Most of them contain natural compounds. It is well known that many people like to customize the therapy choosing "natural" remedies treating PAC, mainly for their children. Consistently, the market data relating to Italy's sales confirm a relevant quote for both dietary supplements and medical devices used to relieve cough and the common cold: the total expenditure is around 200 million per year. Therefore, the current article will present and discuss the most common components in a series of non-pharmacological cough-relievers available in the Italian market as dietary supplements or medical devices (reported in Table 1). It has to be noted that many components belong to traditional western medicine with a consolidated use from a more than millennial tradition for specific substances. In the face of this popular experience, it must be noted that very few substances are supported by scientific evidence provided by randomized controlled trials (RCT).

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Key words: common cold; post-viral acute cough; non-pharmacological remedy; honey; glycerol; herbal medicines.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Received for publication: 25 February 2021.
Accepted for publication: 13 June 2021.

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Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2022; 92:1821
doi: 10.4081/monaldi.2021.1821

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Table 1. List of the most common dietary supplements and medical devices marketed in Italy and with the indication for the cough.

Products	Declared active components	Manufacturing company
Algem Manuka Sed	Manuka honey, Extracts of Althea (<i>Althaea officinalis</i>), Thyme (<i>Thymus vulgaris</i>), Plantain (<i>Plantago major</i> L.), and Grapefruit (<i>Citrus Paradisi</i> Macfad), and Vitamin C (Ascorbic acid).	Algem Natura
Alteafly	Honey, propolis, extracts of Althea and Plantain.	Althea Farmacia
Aluneb Tuss Junior	Snail extract and hyaluronic acid.	Sakura
Arkotos	Glycerol, honey, Arabinogalactans larch (<i>Larix sp.</i>), thyme leaf extract (<i>Thymus vulgaris</i> L.), and agave syrup.	Arkopharma
Balsaben Fitoben	Hydroalcoholic fluid extracts of mountain pine, tolù balsam, eucalyptus, corn poppy, thyme (vulgar and wildflower), polygala, and mint.	Fitoben
Bechiben Fitoben	Hydroalcoholic fluid extracts of corn poppy, licorice, grindelia, elecampane, marshmallow, and mint	Fitoben
Bisolmiel	Honey, marshmallow root, and glycerol.	Sanofi
Bisolvon Duo Emolliente	Honey, dry extract of Altea root, and glycerol.	Sanofi
Broncosulfur	Myrrh, monoterpene, <i>Lavandula Vera</i> and <i>Citrus Reticolata</i> , and N-acetylcysteine.	Laborest Italia
Buona Respiro Sciroppo	Propolis and total polyphenols, Echinacea and echinacoside, zinc gluconate, <i>Rosa canina</i> , and wildflower honey.	Steve Jones
Dicotuss	Honey, extracts of ivy and althea.	Labomar
Dissolmuco	Honey, thyme extract, ivy dry extract, hyaluronic acid, propolis extract, and Eucalyptus essential oil.	Desa Pharma
Droseplus	Tolù balsam, Ipeca, Spongia, Pulsatilla, Coccus cacti, Corallium rubrum, Rumex, Bryonia, and Drosera	Hering
Echinacea Tuss	<i>Echinacea purpurea</i> , altea (<i>Althaea officinalis</i>), linden (<i>Tilia grandifolia</i>), red poppy (<i>Papaver rhoeas</i>), mullein (<i>Verbascum densiflorum</i>), and helichrysum (<i>Helichrysum italicum</i>).	Optima Naturals
Elifly	Alpine snail extract, concentrated raspberry juice, and ascorbic acid.	Princeps
Èqui Benetuss	Acacia honey, extracts of plantain and marshmallow.	Èqui
Eukin	Wildflower honey, extract of <i>Althaea officinalis</i> and <i>Plantago major</i> .	T2A Pharma
Golis Tuss	Hydroalcoholic extracts of mullein flowers, elecampane root (<i>Inula helenium</i> L.), grindelia with flowers (<i>Grindelia robusta</i> , Nutt.), and Drosera grass with flowers (<i>Drosera rotundifolia</i> L.), propolis (Propolis), and essential oils of Eucalyptus (<i>Eucalyptus globulus</i> Labill.) and thyme (<i>Thymus vulgaris</i> L.).	Angelini
Grintuss Syrup	Molecular complex of resins, polysaccharides and flavonoids from grindelia, plantain and helichrysum (Poliresin®).	Aboca
Heliluma	Snail extract and concentrated juice of raspberry juice.	CE.M.O.N
Helix Med Pediatric	Wildflower honey, linden flower extract (<i>Tilia platyphyllos</i> or <i>Tilia cordata</i>), snail mucus extract (<i>Helix aspersa</i>), elderflower dry extract (<i>Sambucus nigra</i>), hydroglycerine extracts of grindelia flower tops (<i>Grindelia robusta</i>) and plantain leaves (<i>Plantago major</i>), essential oils of eucalyptus leaf (<i>Eucalyptus globulus</i>) and pine leaf (<i>Pinus sylvestris</i>).	Pharmalife Research
Kalumax	<i>Helicis pomatie</i> .	Società Natura
Larimucil Bios Line	Honey, concentrated apple juice, arabinogalactans from larch, extracts of plantain grass with flowers, Icelandic lichen thallus, and altea root.	Bios Line
Lichen Sed	Propolis, <i>Cetraria islandica</i> , <i>Uncaria tomentosa</i> , <i>Drosera rotundifolia</i> , and <i>Althaea officinalis</i> .	Promopharma
Limax	Snail drool (<i>Elix Aspersa</i> Muller) and concentrated raspberry juice.	Larix Laboratori
Lisonatural	Honey, extracts of plantain and thyme.	Sanofi
Lumasol	Snail extract, rennet and golden apple juice, and honey.	Fitodorfarma
Manuka Benefit Tuss	Manuka honey, Manuka essential oil, grindelia, Iceland lichen, altea, helichrysum, sundew, primrose, linden, astragalus and calendula.	Optima Naturals
Miele di Manuka Kids Syrup	Manuka honey, Rewarewa honey, essential oils of Manuka, thyme, anise and peppermint, liquorice juice, and glycerin.	Baule Volante e Fior Di Loto
Mucolid	Honey, extracts of altea, drosera, ivy, and snail slime.	Farmaderbe
Mucovit Fluxus	Acacia honey, grindelia flower tops glyceric extract, dry extracts of marshmallow root, fir pine cones, plantain aerial parts, eucalyptus leaves, Scots pine bark, and common thyme leaves, clear juice of red currant, and vitamin C.	Erba Vita Group
Munatoril	Wildflower and eucalyptus honey, lichen, thyme, ivy, ederacoside, plantain, verbascoside and phenols, propolis, galangina, and resveratrol.	Pharmaluce
Pediatuss	Plantago, althea and honey.	Pediatrica Specialist
Petit Drill	Glycerol.	Pierre Fabvre Pharma

To be continued on next page

Antitussive non-pharmacological compounds include different substances, essentially nutrients (honey and its derivatives), vegetal-derivative agents (glycerol, hyaluronic acid, balsamic substances), water solutions, and extracts from plants, such as herbal medicines (Table 2).

Honey and its derivatives

Honey

Honey is a food produced by bees (*Apis mellifera*) from nectar or honeydew. Honey is a supersaturated sugar solution [14]. The

use of honey in medicine dates back to very ancient times [15]. Already around 4000 BC, the Egyptians, and Babylonians used honey to treat respiratory and digestive disorders and soothe the burning of wounds. The ancient Greeks considered honey “the food of the Gods.” Coming to the present day, the World Health Organization recommends honey as a cheap, popular, and safe demulcent to relieve PAC in children [16].

Thanks to its viscosity, the saccharides adhere to the irritated mucous membranes creating a protective film that reduces the stimulus of cough and maintains an adequate hydration state, leading to a soothing effect. Honey also has anti-inflammatory, antioxidant, antibacterial, and metabolic activities [17].

RCTs provided evidence that honey is useful for symptomatic

Table 1. Continued from previous page.

Products	Declared active components	Manufacturing company
APropolaid Flu	N-acetylcysteine, propolis, grindelia, drosera, eucalyptus and mint.	Esi
Propolac	Propolis, <i>Cetraria islandica</i> , <i>Uncaria tomentosa</i> , <i>Drosera rotundifolia</i> , and <i>Althaea officinalis</i> .	Promopharma
S'agapo'	Wildflower honey, dry lime gold extract (<i>Tilia platyphyllos</i> or <i>Tilia cordata</i>), snail mucus extract (<i>Helix aspersa</i>), dried elderberry extract (<i>Sambucus nigra</i>), hydroglycerine extracts of grindelia summit flowering (<i>Grindelia robusta</i>) and plantain leaves (<i>Plantago major</i>), essential oils of eucalyptus leaf (<i>Eucalyptus globulus</i>) and pine leaf (<i>Pinus sylvestris</i>).	S'agapo'
Sedatus Plus	Bearberry, elderflower, rosehip, tamarisk buds, and hornbeam.	Named
Sedatus Minus	Chamomile, bearberry, linden, and hazel.	Named
Sediflu' Tosse Bambini	Eucalyptus honey, extracts of sundew, plantain, ivy, and horehound.	Sakura
Sedituss Tosse Secca	Honey, propolis, hydrolyzed glycosaminoglycans, hydroglycerin extracts of grindelia, mallow, acerola, plantain, and violet.	Desa Pharma
Selentuss	Honey, malva, altea and erisimo.	D.M.G. Italia
Siromucil	Snail extract and concentrated raspberry juice.	Herbit
Stodal	<i>Bryonia cretica</i> , <i>Cephaelis ipecacuanha</i> , <i>Dactylopius coccus</i> , <i>Drosera Mother Tincture</i> , <i>Euspongia officinalis</i> , <i>Kali stibylis tartras</i> , <i>Lobaria pulmonaria</i> , <i>Pulsatilla pratensis</i> , and <i>Rumex crispus</i>	Boiron
Tossvin	Acacia's honey, Tolù balsam (<i>Myroxylon balsamum</i> harms) resin fluid extract, hydroalcoholic extracts of pulmonary (<i>Pulmonaria officinalis</i> L.) aerial parts, poppy (<i>Papaver rhoeas</i> L.) petals, dry extracts of plantain (<i>Plantago major</i> L.) leaves, erisimo (<i>Sisymbrium officinale</i> scop.) aerial parts, Icelandic lichen (<i>Cetraria islandica</i> ach.) thallus; essential oils of eucalyptus (<i>Eucalyptus</i> sp.) and cinnamon (<i>Cinnamomum zeylanicum</i> L.), and ascorbic acid.	Erbenobili
Tuikind	Spongia, antimonium sulfuratum aurantiacum, bryonia, sundew, and ipecacuanha.	Loacker Remedia
Tusserbe Fluid	Mountain pine, plantain, thyme, and mullein.	Esi
Tusserbe Junior	Propolis and Manuka honey, grindelia, pine, plantain, and Icelandic lichen.	Esi
Tusserbe Sed	Red poppy, altea, drosera, lichen, and ivy.	Esi
Tusseval	Honey, propolis, eucalyptus, grindelia, mallow, and echinacea.	Marco Viti Farmaceutici
Tussiflux	Propolis, mallow, plantain, and Icelandic lichen.	Pharma Life Research
Tussil Scioppo	Licorice (<i>Glycyrrhiza glabra</i> L.), grindelia (<i>Grindelia robusta</i> Nutt.), plantain (<i>Plantago lanceolata</i> L.), ed poppy (<i>Papaver rhoeas</i> L.), sundew (<i>Drosera rotundifolia</i> L.), mullein (<i>Verbascum thapsus</i> L.), ivy (<i>Ivy helix</i> L.), black currant (<i>Ribes nigrum</i> L.), black alder (<i>Alnus glutinosa</i> Gaertn.), hornbeam (<i>Carpinus betulus</i> L.), acacia honey, vegetable glycerol, star anise (<i>Illicium verum</i> Hook. F.), scots pine (<i>Pinus sylvestris</i> L.), and grapefruit (<i>Citrus paradisi</i> Macfad.)	Bauer Pharma
Tussil Baby	Whole plant sundew, scots pine buds, primrose flowers, rose petals, cornflower flowers, linden flowers, and purple violet blue petals	Bauer Pharma
Tussilene	Propolis, extracts of altea, erisimo, horehound, and mallow, essential oils of pine, mint, and eucalyptus.	Erbecedario
Tussistin Kind	Drosera and concentrated apple juice	Loacker Remedia
Vivin Tosse	Honey, extracts of marshmallow and plantain.	Menarini
Weleda Melata di Licheni	Honey, <i>Cetraria islandica</i> (L.), <i>Cladonia rangiferina</i> (L.), <i>Usnea barbata</i> (L.), and <i>Lobaria pulmonaria</i> (L.).	WELEDA
Wintuss	Honey, dry extracts of plantain and <i>Viola tricolor</i> , mallow hydroglycerin extract, mint essential oil, and glycerol.	PENSA PHARMA

relief of nocturnal post-viral cough, reducing cough duration and severity, and improving sleep quality for both children and their parents [18-20]. In particular, honey could be useful in reducing the urge to cough reflex as recently envisaged [21]. A meta-analysis concluded that honey probably relieves acute cough in children to a greater extent than no treatment, diphenhydramine, and placebo, but may make little or no difference compared to dextromethorphan [22].

An RCT provided evidence that honey complexed with resins, polysaccharides, saponins, flavonoids, and sugars, appeared superior to carbocysteine and placebo in the treatment of cough persisting more than seven days [23]. A further RCT showed that this syrup significantly improved nocturnal and daytime cough and sleep quality for both children and parents [24].

Notably, it has to be underlined that honey administration is not recommended in children younger than one year for a high risk of infantile botulism [25,26].

As honey derives from the flowers' nectar, its organoleptic properties depend on the individual flower species' characteristics. Actually, most of the kinds of honey are derived from the collection of multi-floral nectar by bees. However, there are selected productions of honey that derive from the supply of specific monofloral nectar. Consequently, many types of monofloral honey exist, each of which can claim to have different beneficial activities. For example, there is a popular belief that linden and eucalyptus honey are a good cough remedy. In this regard, an RCT evidenced that three types of honey (eucalyptus, citrus, and aromatic herbs) were superior to placebo for nocturnal cough in 300 children with upper respiratory infections [27].

There is also evidence for Manuka honey. Manuka honey derives from the flowers of *Leptospermum scoparium*, a plant indigenous by New Zealand and Australia. Manuka honey exerts important bactericidal and anti-inflammatory activity, as demonstrated by a randomized controlled trial [28].

Propolis

Propolis is a resinous mixture that honey bees produce by mixing saliva and beeswax with exudate gathered from tree buds, sap flows, or other botanical sources. It is used as a sealant for unwanted open spaces in the hive. Therefore, propolis exerts bactericidal, and disinfectant activity modulates the immune response and is

Table 2. Main non-pharmacological classes of components used for relieving the post-viral cough and other symptoms of the common cold.

Natural products
Honey (including Manuka honey) as a food
Honey blended with complex extracts of herbal medicines
Propolis
Complex extracts of herbal medicines (usually as a blend)
Glycerol (alone or as syrup ingredient)
Oral herbal medicines (usually as blend)
Nature-derived isolated compounds (glycerol, eucalyptol, menthol, thymol)
Resveratrol
Lactoferrin
Nasal sprays with herbal medicines
Vitamins and oligoelements
Nasal irrigation with saline, thermal water, or hyaluronic acid

commonly used in upper respiratory infections [29]. Propolis may be adequately extracted and fractioned to select the active components, such as pinocembrin, galangine, and acid caffeic ester. There is evidence that propolis components are useful in treating patients with PAC [30-33].

Vegetal-derivative agents

Glycerol

Glycerol is a colorless, odorless, and viscous liquid; it is found naturally in all cells in the form of triglycerides, and it occurs naturally in most products of fermentation [34]. Due to its lubricating and demulcent activity and sweetness, glycerol could contribute up to 85% of cough syrups' benefit [35,36]. The humectant properties of glycerol are due to three hydrophilic alcoholic hydroxyl groups in its chemical structure that can attract and bind to molecules of water and, additionally, to exert a plasticizing effect preventing drying out mucosal dryness. Notably, glycerol administration has not been associated with adverse effects, except in very high concentrations when a dehydrating effect is apparent [37]. Interestingly, the World Health Organization and British Medicines and British Healthcare Products Regulatory Agency promoted the use of cough-reliever syrups containing glycerol [38,39]. It is plausible that the glycerol effectiveness in improving acute cough depends on mechanisms similar to honey. Both compounds exert a relevant demulcent activity.

Notably, glycerol can be used as early as six months of age.

Menthol

Menthol is cyclic monoterpene alcohol with balsamic, analgesic, antifungal, antipruritic, anti-inflammatory, antitussive, antiviral, insecticidal activities exert antitussive effects as is an agonist of the Transient Receptor Potential (TLR) receptors M8 [40]. The freshness sensation is perceived immediately after being placed in the mouth. Menthol is, therefore, commonly present in many cough-reliever products [41-43]. However, it may be toxic at high concentrations [44].

Eucalyptol

Eucalyptol is a cyclic ether and monoterpenoid. It has balsamic, anti-inflammatory, and antioxidant activity [45]. It is popularly used to relieve cough. It acts on TLR receptors [46]. As though menthol, eucalyptol is widely used in many cough-reliever natural products.

Thymol

Thymol is the main monoterpene phenol occurring in essential oils isolated from plants belonging to the *Lamiaceae* family, mainly in *Thymus vulgaris* [47]. Thymol is employed for positive balsamic, antioxidant, anti-inflammatory, local anesthetic, and anti-septic activity to relieve cough [48].

Myrrh

Myrrh is a natural resin derived from the *Commiphora* plant. It is rich in tannins, resins, polysaccharides, and flavonoids; thus, it is used in medicine because of analgesic activity and antitussive activity in children [49]. Its chemical property (resin) is also used to bind plant extracts in some complex natural products.

Resveratrol

Resveratrol is a non-flavonoid phenol and a phytoalexin naturally produced by numerous plants in response to attacks by pathogens such as bacteria or fungus [50]. It has anti-inflammatory, antioxidant, and antiviral activity. Two studies demonstrated that resveratrol effectively relieved cough in children with the common cold [51] and recurrent respiratory infections [52].

Hyaluronic acid

Hyaluronic acid (HA) is a main component of the extracellular matrix and has a crucial role in tissue regeneration and inflammation response [53]. HA is a regular constituent of airway secretions. Indeed, HA is present at the ciliary border of the lining epithelium respiratory mucosa and secretions of the airways; here, HA maintains the airways' physiology, thanks to its peculiar characteristics chemical-physical. The viscoelastic properties of HA and its ability to hydration and lubrication depend on the high molecular weight. Furthermore, being HA, a highly hygroscopic molecule, plays an essential role in modulating surface osmotic balance [54].

In summary, the main actions of HA, especially of high molecular weight, can be identified in: i) hydration (HA thanks to its hygroscopic properties and lubricants, helps keep the hydrated nasal mucosa, a necessary condition for humidifying and purifying the inhaled air; ii) repair (HA has an emollient action and soothing that relieves symptoms caused by irritation or inflammation while promoting processes repair of the respiratory mucosa); iii) protection (HA contributes to maintaining a significant protective barrier against agents external harmful and pathogens), and iv) immunological (HA interact with the CD44 receptor involved in the mechanisms of adhesion and migration of immunocompetent and inflammatory cells and modulates the activity kallikrein-1).

It is commonly used in many products for nebulization or nasal spray. Two studies showed that inhaled hyaluronic acid significantly improved respiratory symptoms, including cough, in children with an acute respiratory infection [55,56].

Table 3. Principal single natural components contained in the dietary supplements and medical devices for the cough. Components with evidence by RCT are in bold.

<i>Agave americana</i>	<i>Malva sylvestris</i>
<i>Aloe vera</i>	<i>Mentha piperita</i>
<i>Althea officinalis</i>	<i>Myroxylon balsamum</i>
<i>Cetraria islandica</i>	<i>Papaver rhoeas</i>
<i>Citrus paradisi</i>	<i>Pelargonium sidoides</i>
<i>Citrus reticulata</i>	<i>Pinus mugo</i>
<i>Drosera rotundifolia</i>	<i>Plantago major</i>
<i>Echinacea purpurea</i>	<i>Polygala</i>
<i>Eucalyptus globulus</i>	<i>Populus nigra</i>
<i>Glycyrrhiza glabra</i>	<i>Ribes nigrum</i>
<i>Grindelia robusta</i>	<i>Rosa canina</i>
<i>Hamamelis virginiana</i>	<i>Salvia officinalis</i>
<i>Hedera helix</i>	<i>Sambucus nigra</i>
<i>Helichrysum italicum</i>	<i>Thymus vulgaris</i>
<i>Helix pomatia</i>	<i>Tilia platyphyllos</i>
<i>Helix aspersa</i>	<i>Uncaria tomentosa</i>

Water solutions

Saline solution

Upper airways should be clean and open to regular function [57]. Hypersecretion of mucus causes posterior rhinorrhea that in turn causes the post-nasal drip. Secretion dripping triggers irritant receptors and, as a consequence, elicit cough reflex. Saline irrigation or nasal spray, using the isotonic or hypertonic formulation, is commonly used in children with upper respiratory infections [58-61]. Also, thermal water is useful in treating upper airway diseases, relieving cough [62]. Notably, salsobromiodine thermal water may be added with natural substances and hyaluronic acid to improve its efficacy, as recently demonstrated [63,64].

Moreover, the saline solution may be frequently combined with active components, such as hyaluronic acid and/or plant extracts, with synergic effects. Noteworthy, as PAC depends on the accumulation of secretions, their removal could represent a necessary treatment in infants less than six months of age. Nasal washing and humidification are the only safe, effective procedures adopted in infants with PAC.

Plant extracts

Traditional western medicine is a popular remedy to treat common cold symptoms and, in particular, cough. Many plant extracts are used, even though the rationale is frequently based on the empirical ground. However, some recent studies provided evidence that some components are effective in relieving post-viral acute cough. In this regard, the European Medicine Agency recognized the validity of some natural compounds and started a regulatory function to define recommendations collected in a monograph [65]. EMA selected some plants effective in cough relief. Here, we present, in alphabetic order, some plant extracts whose clinical efficacy has been documented. These components are common ingredients of products available as a medical device or dietary supplement, as reported in Table 1 and 3.

Adhatoda vasica (Justicia adhatoda)

Adatoda is a medicinal plant of the *Acanthaceae* family, a native of Asia. The active ingredients are alkaloids (vasicine, vasicin N-oxide, vasicinone, deoxivasicin, mayiontone), essential oil, and adatodic acid [66]. Adatoda has bronchodilator, antihistaminic, expectorant, mucolytic, and antiseptic activities. The primary active alkaloid, vasicine, and its self-oxidation product, vasicinone, produce prolonged bronchodilation comparable to that obtained with theophylline, due in part to depression of the vagal nerve endings at the bronchial level, in part to a true antihistamine stabilizing action, decreasing the resistance to respiratory flow [67]. The essential oil with the alkaloid principles acts by depolymerizing the mucoproteins (the mucus dissolves becoming less dense) and stimulating the respiratory system (thus favoring the mucus' clearance itself).

Adatoda is indicated to relieve cough [68]. An RCT showed a fixed combination of aqueous ethanolic extracts of *Justicia adhatoda* leaf, *Echinacea purpurea* root, and *Eleutherococcus senticosus* root exerted significant antitussive effects in patients with an upper respiratory infection [69].

Agave americana

Agave is a succulent plant typical of tropical countries and belongs to the *Agavaceae* family. Agave contains volatile oil, agave gum, phloionolic acid, oxalic acid, oxalates of various kinds, a saponin (echogenin), sugars (in particular agavose), pectins, and resins. Agave is a healing plant, used for a long time as a remedy in folk medicine; fresh and dried leaves exert an anti-inflammatory action and calm irritations. A study compared agave nectar, placebo, and no treatment in infants and toddlers with acute cough. Interestingly, the placebo effect was significantly superior to no cure, and there was no additional benefit offered by agave nectar [70]. This outcome is very relevant as underline the placebo's therapeutic value and highlights the need to perform RCT with a placebo arm.

Aloe vera

Aloe belongs to the *Aloaceae* family. The use of aloe is very ancient, as evidenced by the cuneiform text of some clay tablets found in the Mesopotamian city of Nippur, near Baghdad, Iraq, and datable to around 2000 BC. In a tablet, it was written: the leaves looked like sheaths of knives. Aloe was also known and used by the Egyptians (as mentioned in the "Ebers papyrus" of 1550 BC). There is a popular thought that aloe has many beneficial properties. Agave regenerates the damaged mucosa and exerts anti-inflammatory, moisturizing, hydrating, analgesics, fungicide, antiviral, antibacterial, hemostatic, and lenitive: relieves itching [71]. However, no study investigated its efficacy in subjects with PAC.

Althea officinalis

Marshmallow belongs to the *Malvaceae* family. The juice is the main ingredient and is extracted from the root. The high content of mucilage explains the emollient, laxative, and calming properties. *Althea officinalis* is used for the treatment of cough for centuries. The topical application of marshmallow roots' medicinal extracts shows immediate effects like a protective film on the inflamed mucosa. The soft layer reduces the mucosa's irritation and protects the respiratory tract from environmental injury, including viral infections. An in vitro study demonstrated anti-inflammatory and antioxidant activity on macrophages [72]. Moreover, marshmallow has expectorant and antitussive effects. A recent review stated that the results of animal and clinical studies confirmed the efficacy of *A. officinalis*, combined with other plant extracts, in the treatment of cough [73].

Cetraria islandica

Icelandic lichen is a species of fruticose terricolous lichen typical of the lava fields in Iceland. The thallus contains: polysaccharides (lichein and isolichein), bitter lichenic acids (usnic and cetraric acid), folic acid, and other vitamins of group B. Usnic acid gives the plant an antimicrobial and antiseptic activity useful in the presence of respiratory diseases. Lichenin produces mucilage, a jelly, with marked mucolytic, decongestant, and expectorant action [74]. However, no study investigated its efficacy in subjects with PAC.

Citrus paradisi

Grapefruit is a fruit tree belonging to the genus *Citrus* and the *citris* family. Some studies highlight the broad-spectrum antifungal, antimicrobial and antibacterial properties of grapefruit seed extract [75]. It has been reported that the seeds fight more than 800 different types of bacteria and viruses [76]. Besides, it contains hesperidin, a flavonoid with antioxidant, anti-inflammatory, and immunomodulating properties [77]. Therefore, grapefruit seeds are

thought to be useful for treating common cold symptoms, including cough. Two studies confirmed this activity [63,64].

Citrus reticulata

Mandarin is a fruit tree belonging to the genus *Citrus*. The peel of the mandarin contains limonene, an antioxidant substance [78]. In Traditional Chinese Medicine, mandarin is included in the classification of therapeutic foods, namely, the infusion with mandarin zest is indicated for cough. However, no study investigated its efficacy in subjects with PAC.

Drosera rotundifolia

Sundew is a carnivorous plant of the *Droseraceae* family. It contains significant amounts of polysaccharides and polyphenols, mainly quercetin and isoquercetin [79,80]. The leaves of sundew are used to relieve cough thanks to the flavonoids and derivatives of ellagic acid [81]. Also, the extracts of the aerial parts have antimicrobial activities. *Drosera* produces various secondary metabolites, including naphthoquinones, which displays anti-inflammatory and antimicrobial properties [82]. A homeopathic drug-containing also extracts sundew was superior to placebo in relieving acute dry cough in children [83].

Echinacea purpurea

This plant's medicinal use is lost in time: the Amerindians of North America used the rhizome to treat wounds and various skin diseases, wounds from trauma, from snake bites, smallpox, measles, epidemic mumps, arthritis, and preparation of mouthwashes.

The modern pharmacopeia has extended popular knowledge by attributing a role in strengthening the immune defenses. *Echinacea* can also be used for the treatment of the common cold. The European Medicines Agency (EMA) has approved *Echinacea purpurea* flower extract for the short-term prevention and treatment of common cold [65]. The agency recommends that it should not be taken for more than ten days. Administration to children under the age of 1 year is contraindicated due to possible side effects on an immature immune system.

Moreover, children between 1 and 12 years of age are not recommended, as the efficacy has not been sufficiently documented [84]. In the absence of sufficient data, use during pregnancy and lactation is not recommended. The British Medicines and Healthcare products Regulatory Agency has expressly advised against *Echinacea*'s administration to all children under the age of 12 due to the risk of developing severe allergic reactions; risk which, although not frequent, remains higher than that of any expected benefits.

A meta-analysis concluded that the use of different *Echinacea* preparations prevents subsequent upper respiratory infections in children [85]. However, a more recent Cochrane meta-analysis concluded that *Echinacea* products had not been shown to provide benefits for treating the common cold symptoms, although there may be a weak benefit from some *Echinacea* products [86]. The results of individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance [85]. A systematic review and meta-analysis evaluated *Echinacea*'s role in treating cough and revealed limited evidence for this plant [88].

Eucalyptus globulus

Eucalyptus is an evergreen tree of the *Myrtaceae* family. The essential oil is extracted by steam distillation of the fresh leaf. It is composed of about 70% cineole. It is used in many multi-compo-

ment products for relieving cough. A multi-component product containing camphor, menthol, and eucalyptus oils in a petrolatum base, was superior to petrolatum alone or no treatment in reducing cough in children [87].

Glycyrrhiza glabra

Licorice is a perennial herbaceous plant belonging to the *Fabaceae* family. The most important active ingredient in licorice is glycyrrhizin, which plays anti-inflammatory and antiviral action. Glycyrrhizin exerts anti-inflammatory activity by modulating the production of inflammatory cytokines, inhibiting reactive oxygen species accumulation, reducing inflammatory exudates, and increasing the production of endogenous interferon [88]. Moreover, glycyrrhizin binds to a pocket of HMGB1 protein, preventing the link with its receptor. HMGB1 protein is a nuclear protein belonging to the group of damage-associated molecular patterns. These proteins are released into extracellular liquid after cell damage, and they amplify the message of damage occurred, inducing the activation of the immune cells [89]. In this context, glycyrrhizin's topical use significantly reduced two important pro-inflammatory cytokines, TNF- α and IL-1 β [90].

Moreover, the complex glycyrrhizin-HMGB1 effectively reduces the inflammatory infiltrate [91]. Glycyrrhizin also has antiviral activity [92]. Licorice contains a potent antitussive compound (liquiritin apioside) whose antitussive effect may depend on peripheral and central mechanisms [93]. An RCT showed that glycyrrhizin therapy was associated with shorter hospitalization, lower-grade fever, and lower treatment cost than placebo in patients with viral upper respiratory infections [94].

Grindelia robusta

Grindelia robusta is a medicinal herb of the sunflower family that is composed of different diterpenoid natural products. Its major constituents are grindelic acid and related grindelane diterpenoids [95]. It exerts expectorant, antitussive, and anti-inflammatory activity. Traditionally, it was used by Californian indigenous populations to relieve cough.

In a commercial product, *Grindelia* is combined with other plant extracts, including *Helichrysum* and *Plantago*, and honey. Two RCTs provided positive outcomes in children with post-viral acute cough [27,28].

Hamamelis virginiana

Hamamelis virginiana belongs to the *Hamamelidaceae* family. It contains abundant tannins, triterpenes, and flavonoids. It has antiviral, antioxidant, and anti-inflammatory activity [96-98]. A natural product contains extracts from *Hamamelis* and *Thymus*, particularly abundant of tannins and flavonoids. These components are associated with rock salt. However, no study investigated its efficacy in subjects with PAC.

Hedera helix

Common ivy is a plant belonging to the *Araliaceae* family. The main components of ivy are saponins, a group of active ingredients that lowers mucus' surface tension, making it thin. The ivy also contains essential oils, which have a bactericidal action, and tannins, with astringent activity. Some studies explored its cough-relieving activity.

A study showed that an herbal medicine containing ivy leaf dry extract administered twice a day in 5162 children with productive cough significantly reduced cough [99]. A prospective, open, non-interventional study was conducted at 25 medical practices

throughout Switzerland to compare a syrup containing ivy leaf extract acetylcysteine with acetylcysteine in children and adults with cough [100]. The ivy leaf extract was significantly better than acetylcysteine in reducing cough attacks and improving cough-associated sleeping disorders. A placebo-controlled RCT showed that granules containing ivy extract significantly improved cough and common cold symptoms in children [101].

An open study evaluated a combined herbal preparation containing ivy and thyme extracts in patients with acute respiratory infection [102]. This compound reduced cough and expectoration.

Helichrysum italicum

Helichrysum italicum belongs to the *Asteraceae* family. *Helichrysum*'s main action is antioxidant, thanks to the high content of polyphenols, flavonoids, and coumarins. These substances protect against the ROS free radicals [103]. *Helichrysum italicum* acetophenones, flavonoids, and phloroglucinols demonstrated inhibitory action in different arachidonic acid metabolism pathways and other pro-inflammatory mediators [104]. Therefore, it is used to treat cough in traditional medicine [105].

Helix pomatia* and *Helix aspersa

Snail syrup can be formulated with extracts of *Helix pomatia* (also known as a Burgundian snail or vine grower) or with extracts of *Helix aspersa* (or knurled snail), both gastropod mollusks belonging to the *Helicidae* family [106]. The extracts of these snails contain mucopolysaccharides with fluidifying and expectorant properties [107]. These extracts are included in some multi-component syrups for cough. However, no study investigated its efficacy in subjects with PAC.

Malva sylvestris

Wild mallow is a plant belonging to the *Malvaceae* family. The name derives from the Latin mallow and has the meaning of springs because its emollient properties have been recognized since ancient times. In particular, the flowers and the leaves of the mallow are rich in mucilage, terpenoids, and phenols, with emollient and anti-inflammatory properties [108]. These active ingredients work by coating the mucous membranes with a viscous layer that protects them from irritants. For this reason, the use of mallow is indicated against cough and the common cold. However, no study investigated its efficacy in subjects with PAC.

Marrubium vulgare

The horehound is a small herbaceous perennial plant with labiate flowers belonging to the *Lamiaceae* family. The plant contains essential oil, triterpenes, flavonoids, polyphenols, bitter substances, tannins, sesquiterpene lactones, and mucilage [109]. Horehound is used as a mucolytic and cough suppressant [110]. The primary mechanism is linked to forming a protective film on the mucous membranes, thanks to mucilage [111].

Mentha piperita

Peppermint is a perennial herbaceous plant, stoloniferous, intensely aromatic, which belongs to the *Labiatae* family (*Lamiaceae*) and the genus *Mentha*. The main components of mint are an essential oil rich in menthol and menton, enzymes (oxidase and peroxidase), C vitamin, phenolic acid, caffeic acid, flavonoids, and tannins [112]. Traditional medicine recognizes expectorant, balsamic, analgesic, and antiseptic (antibacterial and antiviral) activities. A randomized study compared a spray containing aromatic essential oils of five plants (*Eucalyptus citriodora*, *Eucalyptus glob-*

ulus, *Mentha piperita*, *Origanum syriacum*, and *Rosmarinus officinalis*) as applied five times a day for three days with a placebo spray in patients with upper respiratory infections [113]. The product was significantly effective in relieving symptoms 20 minutes after administration, but not after three days of treatment.

Myroxylon balsamum

Myroxylon balsamum is a tree of the *Fabaceae* (or *Leguminosae*) family, widespread in tropical areas and Polynesia. The balsam of Tolù is obtained from this plant, from the Colombian town of Tolù. About 80% of the oleoresin contains benzoic and cinnamic esters of tolu resin-tannol. The drug has a fair amount of free benzoic and cinnamic acid. There are also esters, such as benzyl benzoate and cinnamate, a small amount of vanillin. Eugenol, ferulic acid, and triterpenoids increase the fluidity of secretions, exerting a balsamic effect. It supports eutrophism of the mucous membranes [114]. However, no study investigated its efficacy in subjects with PAC.

Papaver rhoeas

The common poppy is an annual herbaceous plant belonging to the *Papaveraceae* family and is one of the oldest remedies in popular herbal medicine. It has always been used for its sedative properties of coughs, which calm spasms, favor expectoration, and facilitate sleep. In the petals were found low quantities of alkaloids: isoquinolic alkaloids (0.7%) of which roeadin (tetrahydrobenzazepine) is the majority [115]. This alkaloid was found in all parts of the plant except the seeds. There are other alkaloids in the aerial parts, such as protopin (also in the roots), captisin, sanguinarine, chelitrina, anthocyanin glycosides (mecocyanine, cyanine, and others), and mucilage. The seeds contain fatty oil (35%), mainly linoleic, oleic, palmitic, and stearic acids. Popular medicine attributes to Roeadin sedative and cough-relieving properties useful to treat common cold [116].

Pelargonium sidoides

Pelargonium belongs to the *Geraniaceae* family. The extract of the roots of this geranium contains secondary compounds, including coumarin derivatives (umckalin), gallic acid and its esters, flavonoids (quercetin), flavan-3-ols (catechins), and phytosterols. *Pelargonium* extract reduces the use of antibiotics for acute respiratory infections [117]. Moreover, *Pelargonium* has antiviral and antibacterial effects, modulates the release of TNF- α and nitric oxides, stimulates interferon- β , and increases natural killer cell activity [118]. A meta-analysis found 11 RCTs exploring the *Pelargonium* activity in patients with post-viral cough [119]. The level of evidence was considered moderate (RR=4.6).

Pinus mugo

The mountain pine, or simply mugo, is an evergreen needle-like bush, with a prostrate habit, belonging to the *Pinaceae* family. The essential oil contains terpene compounds and esters (for 4-10%), especially bornyl acetate; the leaves contain esters, resins, and glycosides [120]. The essential oil has antiseptic and mucolytic properties; it can also be used to carry out fumigations with hot water in cough, cold, and phlegm [121].

Plantago major

Plantain belongs to the *Plantaginaceae* family. It contains polysaccharides and polyphenols with antibiotic activity [122]. Plantain leaves contain iridoid glycosides, flavonoids (luteolin),

mucilage, tannins, pectins, and salic acid. These active components give plantain antitussive, expectorant, antibacterial, anti-inflammatory, and astringent properties. The anti-inflammatory action of plantain is due to the aucubin, in which hydrolysis releases a bicyclic genin, called aucubigenin [123]. This active ingredient has a marked antiallergic and decongestant property, whose mechanism of action is expressed in inhibiting the synthesis of pro-inflammatory mediators [124]. Plantain is traditionally used in traditional Persian medicine to relieve cough [125].

Polygala

Polygala is a genus of spermatophyte Dicotyledonous, arboreal, herbaceous, climbing, and perennial plants, belonging to the *Polygalaceae* family. The etymological origin of the name of the plant dates back to an ancient belief. It was thought that this botanical species was able to stimulate the production of milk in cows. *Polygala*, in Greek, really means 'much milk.' This belief was then extended to pregnant women, thinking that it could stimulate milk's secretion in abundance. The *polygala* contains saponins, triterpenes (senegine), flavonoids, salicylic acid, tannins, and resin [126]. The *polygala* has mucolytic and expectorant activity, conferred mainly by the saponins. Native Americans use this plant as an anti-inflammatory remedy for the treatment of common colds [127].

Populus nigra

The black poplar is a tree species of the genus *Populus*. The constituents of the poplar tree are glycosidic derivatives (salicin, salicortin), benzene derivatives (tremuloidin, populin), tannins, trisaccharides, triterpenes, and resins [128]. Anti-inflammatory, antioxidant, balsamic, and expectorant activities, counteract cough, and phlegm [129].

Ribes nigrum

Blackcurrant (is a plant belonging to the *Grossulariaceae* family. The buds are rich in essential oil, flavonoids, and glycosides. Blackcurrant has a cortisone-like activity by increasing the production of adrenal steroids [130]. Therefore, the blackcurrant bud extract is used for its natural anti-inflammatory and antihistaminic property that acts on the respiratory tract. The pulp is rich in anthocyanosides, belonging to the flavonoid family, mirtillin, tulipanin, chrysanthemum, and antirrinin [131]. The traditional medicine recommends blackcurrant for the common cold and cough [132].

Rosa canina

Sweetbriar is a plant belonging to the *Rosaceae* family. It is the most common spontaneous rose species in Italy, very frequent in hedges and on the edges of woods. Sweetbriar contains L-ascorbic acid, pectins, tannins, essential oil, carotenoids, anthocyanosides, and flavonoids [133].

Rosa canina extracts are used as antioxidants, immunomodulators, vitamins, antiasthenics, and adjuvants in flu syndromes [134]. The extracts are recommended for cough and the common cold.

Salvia officinalis

Common sage is a small herbaceous perennial plant with delicate labiate flowers belonging to the *Lamiaceae* family. The plant contains flavonoids, essential oil (ketones, borneol acetate, pinene, and camphor), derivatives of caffeic acid (chlorogenic and rosmarinic acid), diterpenes and triterpenes, and tannins [135]. Sage is a plant with some therapeutic properties, such as antibacterial, antifungal, antiviral, and astringent [136]. Traditional medicine uses sage for common cold and cough [137].

Sambucus nigra

The elder is a dicotyledonous angiosperm plant belonging to the *Adoxaceae* family and the genus *Sambucus*. The elder has medicinal-herbal properties in fruits and flowers. All the rest of the plant (including seeds) is poisonous since it contains the glycoside sambunigrin. The flowers contain tannins, unrtoside, and the glucoside sambunigrin. The fruits contain tannins, pectins, traces of essential oil, organic acids, and mineral trace elements [138,139]. Elderberry has been used in folk medicine for centuries to treat influenza, common cold, and sinusitis and has been reported to have antiviral activity against influenza and herpes simplex [140].

An RCT investigated the efficacy and safety of oral elderberry syrup for treating influenza A and B infections [141]. Symptoms were relieved, on average, four days earlier, and the use of rescue medication was significantly less in those receiving elderberry extract than placebo. Another RCT significantly reduced the common cold duration and severity in air travelers [142]. A recent review suggested that *S. nigra* berry (in extract or lozenge formulation) may reduce influenza-type symptoms, including fever, headache, nasal congestion, and rhinorrhea, when taken within the first 48 hours of symptom onset [143]. Within 2-4 days of *S. nigra* treatment, most patients experienced significant symptom reduction by an average of 50%. Evidence regarding the effectiveness of *S. nigra* berry on the symptom of cough and the need for/use of medicines (including antibiotics) to treat acute respiratory infections is currently unclear and inconsistent. A meta-analysis reported that supplementation with elderberry was found to reduce upper respiratory symptoms substantially [144]. The meta-analysis suggested that the reported outcomes might be an alternative to antibiotic misuse for upper respiratory symptoms due to viral infections and a potentially safer alternative to prescription drugs for routine cases of the common cold and influenza [145].

Thymus vulgaris

Thyme is a genus of plants of the *Lamiaceae* family. Thyme contains flavonoids and essential oils, including thymol, carvacrol, borneol, linalol, and pinene. Its extracts are traditionally used to relieve cough. It has anti-inflammatory, antiseptic, antibacterial, antioxidant, antimicrobial, and immune-stimulating activity [146,147]. Thyme extracts combined with other herbal plants have been tested to show significant relieving cough [148-150].

Tilia platyphyllos

The linden is a genus of arboreal or shrubby plants of the *Tiliaceae* family.

Flowers with bracts contain flavonoids, including glycosides of quercetin and kaempferol, tannins, mucilage, aromatic (caffeic, chlorogenic, gallic) and organic acids (malic, tartaric, acetic), and essential oil; the sapwood contains: phenolic acids, tannins; and the gemes contain auxins, gibberellins, and growth factors [151]. Linden extracts have anti-flu, antipyretic, sedative, expectorant, and mucolytic properties [152].

Uncaria tomentosa

Uncaria is an original plant of the Peruvian jungle and a liana of the *Rubiaceae* family, named for the thorns that resemble cats' nails. The root and bark of this plant contain phenolic alkaloids, healing agents, antacids, oxindol alkaloids, glycosides of quinovic acid, polyhydroxylated triterpenes [153]. The Uncaria has immune-stimulating, antiviral, anti-inflammatory, and antimutagenic properties [154]. Uncaria is used in phytotherapy in treating chronic inflammatory diseases, immune deficiencies, in the pres-

ence of viral infections, and the prevention and treatment of common cold with fever and cough [155,156].

Conclusions

There is evidence that some non-pharmacological substances significantly improve post-viral acute cough and reduce common cold-dependent symptoms. This evidence confirms the popular tradition of using natural compounds to relieve cough and the common cold favorably. However, many natural components have not been sufficiently investigated. Further studies should be addressed to respond to this unmet need.

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