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Novel Antitussive Agents from Natural Source-A Review

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ABSTRACT

Cough, acts as the defender of the foreign materials and secretions from the airways. Cough gives the protection of the lungs and distal parts of airways from chocking and infected mucus. Cough is one of the major worldwide problem as patients suffering from this visit physician. In this way it leads to the economical problem in the society. The mostly used and available antitussive agents in the markets are codeine and dextromethorphan. Although they are good cough suppressing but they have also numerous side effects e.g., sedation, nausea, addictive potential, and constipation. Although a new class of antitussive drugs are not coming into the market for a long time. To solve this problem pharmacists and researchers are searching novel, less toxic, more effective antitussive drugs from the nature. Plant derived medicines act as the supplementary to the synthetic drugs followed by engineered protein and gene therapy. In this context pharmacotherapy provides some novel alkaloids, triterpenoids, phenolglycosides, polysaccharides, flavonoids, as more effective and less toxic antitussive agents. These said phytochemicals isolated from botanical source play a major role in the treatment of many respiratory diseases including cough. Some of the above mentioned extracts from the shrubs are used in the Indian traditional medicine, they can be used as a safe antitussive agents. These provide a scientific basis to the Indian traditional medicine to be used as a novel antitussive agents as well as expectorant in the remedy of cough problems.

KEY WORDS: Antitussive activity, Polysaccharides, Arabinogalacatan, Alkaloids, flavanoids, triterpenes, Cough.

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INTRODUCTION

Cough, a indispensable physiological reflex that acts as a defender of the foreign materials and secretions from the airways. In this way it protects the lungs and distal parts of airways from chocking and infected mucus[1]. The largest part of the world is suffering from Cough. So antitussives are the extensively used medications in the world. The everyday life of the patient is fatally affected by the cough. It is also responsible for the substantial financial burden to our society[2]. According to Bolser, 1996[3], currently available antitussive drugs are mainly classified into the two categories. Firstly, central antitussive drugs (drugs acting on central nervous system) and secondly, peripheral antitussive drugs (drugs acting on elements of peripheral nervous system). The most commonly used central antitussive agent codeine and dextromethorphan show potential efficacy towards cough. But these two drugs have some adverse effects like sedation, nausea, addictive potential, and constipation[1]. When Dextromethorphan is taken in high dose, it causes neurological, cardiovascular and gastrointestinal problems[4]. The two opiate antitussives codeine and morphine have some addiction property[5]. The peripheral antitussive agents moguisteine and levodropropizine show less side effects[6]. A new class of safe antitussive agent is unavailable from the market for a long time. So there is a need to develop novel, less toxic, strong antitussive drugs in the field of pharmaceutical chemistry[7]. Numerous studies on the usage of the medicinal plant materials reveal that nature is the important resource of new and semi-synthetic drugs. In this way the botanical source of nature is continuously playing a major role as a supplier of novel, less toxic antitussive agents[8,9]. The phytochemicals from plant source mainly polysaccharides, flavanoids, alkaloids play a major role in the treatment of many respiratory diseases including cough. It is reported that the arabinogalactan and arabinogalactan protein (AGP) isolated from Indian plants *Adhatoda vasica, Withania somnifera, Glycyrrhiza glabra, Psidium guajava, Piper nigrum, Nyctanthes arbor-tristis, Solanum virginianum, Andrographis paniculata* show promising antitussive activity in vivo[10-17]. They did not show any adverse effects during the experiment. So they can be assumed as safer antitussive agents in near future[19].

Besides polysaccharides, some alkaloids are also exhibit antitussive property. Wang et al., 2011[20] isolated four promising antitussive alkaloids imperialine, chuanbeinone, verticinone, and verticine from the *Bulbus Fritillariae Cirrhosae* (BFC) using phytochemical method. Wang and his group in 2012[21] also isolated four more antitussive alkaloids imperialine, imperialine-N-oxide, isoverticine, and isoverticine-N-oxide isolated from Bulbus of *Fritillaria wabuensis* BFW.

The use of aerial parts of *Peganum harmala Linn* (APP) as a traditional Chinese medicine for the treatment of the cough and asthma is reported. Two alkaloids namely Quinazoline and beta-carboline

and two flavanoids deacetylpeganetin and peganetin are the main chemical ingredients in *Peganum harmala linn* (APP). The alkaloid fraction of the APP is mainly responsible for the treatment of respiratory diseases[22].

Shou et al., 2018[23] isolated of novel antitussive biflavonoids from *Cardiocrinum giganteum* seeds. The active chemical constituents are CGY-1 and CGY-2 belong to biflavone-type chemicals, a subgroup of flavonoids.

The antitussive activitity of the aqueous extract, 50% ethanolic extract, 70% ethanolic extract, and 90% ethanolic extract of *Citri grandis* is reported by Jiang et al., 2014[24]. Out of these said four extracted fractions 70% ethanolic extract of demonstrated the significant effects in vivo. Although bioactive constituents and the mechanism of antitussive, expectorant activity of these said four fractions are not reported by Jiang et al., 2014[24].

Barth and his group in 2015[25] prepared the Kan Jang ® oral solution (KJ) for the treatment of the upper respiratory tract infections (URI). They had prepared this solution by the fixed combination of aqueous ethanolic extracts of *Justicia adhatoda* L. leaf, *Echinacea purpurea* (L.) Moench root, and *Eleutherococcus senticosus* (Rupr. & Maxim.) Harms root. Kan Jang ® oral solution (KJ) exhibit significant antitussive effects in URI and has a good tolerability profile. It is an approved herbal medicinal product for URI in Scandinavia[25].

Ethanolic extract of *Clitoria ternatea* flowers (ECT) exhibits the anti-allergy and anti-tussive potential. This extract contains flavonoids, alkaloids, tannins, cardiac glycosides anthraquinones, saponins and phenols[26]. The essential oil isolated from the decoction of the *Blepharocalyx salicifolius* leaves shows potential antitussive, antispasmodic, bronchodilating activity in vivo and also used in the South America for the treatment of the cough and bronchospasm[27].

The extensive use of *Farfarae Flos* (FF) in the treatment of cough, bronchitis, and asthmatic disorders as a Traditional Chinese Medicine (TCM) is well documented. The pharmacologically active (antitussive activity and expectorant effect) chemical constituents in FF are 4,5-O-dicaffeoylquinic acid, caffeic acid, chlorogenic acid, 3,5-O-dicaffeoylquinic acid, 3,4-O-dicaffeoylquinic acid, rutin, kampferol analogues, 2,2-dimethyl-6-acetylchromanone, EMDNT, tussilagone, Bauer-7-ene-3β,16α-diol, β-sitosterol, sitosterone[28]. The use of licorice as an potent antitussive and expectorant in the ayurvedic medicines from the ancient time. Liquiritin apioside, liquiritin, liquiritigenin are active chemical constituents which reduce significantly cough frequency. The antitussive activities depend on both peripheral and central mechanisms[29].

This review will discuss about the some novel antitussive agents and expectorants from the natural resource mainly from the plant source and their structure, antitussive activity and their mechanism of actions.

Types of currently available antitussive drugs and their actions on cough

The unmet clinical problem cough is the symptoms of asthma, chronic obstructive pulmonary disease, gastroesophageal reflux. There are many types currently used antitussive drugs in the market. They are H1-Receptor Antagonists, Dextromethorphan, Opiates: Codeine and Morphine, Local Anesthetics, Caramiphen, Carbetapentane or Pentoxyverine, Levodropropizine. Besides this there are other types of drugs which have effect on the cough. They are Menthol and TRPM8 Agonists, Erdosteine, Antibiotics, Glucocorticosteroids, β_2-Agonists, Muscarinic Receptor Antagonists, Mucolytics and Expectorants, Antacids/Proton Pump Inhibitors and Gastrointestinal Motility Drugs, Xanthines, Cromones.

The examples of the above discussed drugs are summarized into a Table-1and Table-2.

Table-1:- List of the currently used Antitussive drugs into the market

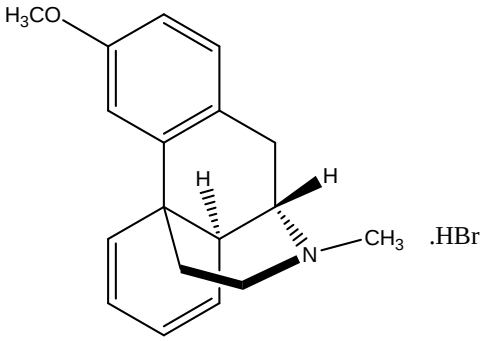
Name of Drug	Types of drug	References
Diphenhydramine	H1-Receptor Antagonists	Packman et al., 1991[31]
Dextromethorphan HBr [(+)-3-Methoxy-17-methylmorphinan hydrobromide monohydrate]	Dextromethorphan	Delgado and Remers, 1998[32]; Mabasa and Gerber, 2005[33]
Codeine and Morphine	Opiates	Takahama and Shirasaki, 2007[34]; Molassiotis et al., 2010[35]
lignocaine/lidocaine	Local Anesthetics	Hansson et al., 1994[36]
Benzonatate	Local Anesthetics	Molassiotis et al., 2010[35]
Caramiphenedisylate	Caramiphen	Domino et al., 1985[37]
2-[2-(Diethylamino)ethoxy]ethyl 1-phenylcyclopentanecarboxylate	Carbetapentane or Pentoxyverine	Brown et al., 2004[38]
1-Phenyl-1-(o-chlorophenyl)-3-dimethylamino-propranol-1 hydrochloride	Chlophedianol	Diwan et al., 1982[39]
Levodropropizine	Nonopioid	Bossi et al., 1988[40]
Menthol	Menthol and TRPM8 Agonists	Wise et al., 2012[41]
Erdosteine	Homocysteineanalog	Cazzola et al., 2010[42]
Erythromycin, Amoxicillin, Doxycycline	Antibiotics	Braman, 2006a[43]; 2006b[44]
Beclomethasonedipropionate	Glucocorticosteroids	Gillissen A, et al., 2007[45]
Salbutamol (Albuterol)	β2-Agonists	Mulrennan S et al., 2004[46]
Ipratropium bromide	Muscarinic Receptor Antagonists	Holmes P.W et al., 1992[47]
Guaifenesin	Mucolytics and Expectorants	Dicpinigaitis P.V. et al., 2003[48]; 2009[49]
Erythromycin and Azithromycin,	Antacids/Proton Pump Inhibitors and Gastrointestinal Motility Drugs	Moshiree et al., 2010[50]
Theophylline	Xanthines	Dubuis et al., 2014[51]
Disodium cromoglycate	Cromones	Mackay G.A. and Pearce F.L. 1996[52]

Now a days the new approaches of cough treatment are introduced into the market. This new approach includes Levocloperastine, Amitriptyline, Novel N-Methyl-D-aspartate Receptor Antagonists, Glaucine, Moguisteine, Phosphodiesterase Inhibitors, K^+ Channel Openers, Cl^-Pump Inhibitors, Ouabain-Sensitive Na^+-K^+ ATPase Inhibitors, Leukotriene Receptor Antagonists, Interferon-α, Tropan Derivatives with High Affinity for the Nociceptin Opioid Receptor (Nociceptin), Selective Cannabinoid 2 Receptor Agonists, Neurokinin Receptor Antagonists, Transient Receptor Potential Vanilloid 1 Receptor Antagonists, Transient Receptor Potential A1 Receptor Antagonists, VRP700, GABA Receptor Agonists, E121, Gabapentin, Thalidomide, Botulinum A Toxin, Na_V Channel Blockers, P2X2/3 Antagonists[30].

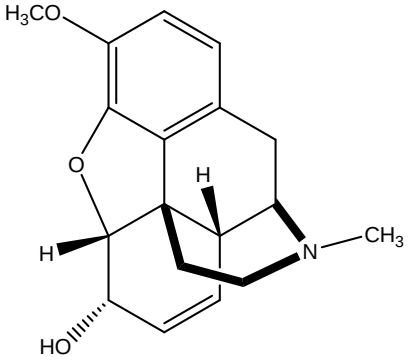
Table-2:- List of the Newly approached Antitussive drugs into the market

Name of Drug	Types of drug	References
1-[2-[(4-chlorophenyl)-phenylmethoxy]ethyl]piperidine	Levocloperastine	Catania and Cuzzocrea, 2011[53]
Amitriptyline	Amitriptyline	Jeyakumar A. et al., 2006[54]
Memantine	Novel N-Methyl-D-aspartate Receptor Antagonists	Canning, 2009[55]
Glaucine	Alkaloid	Dierckx P et al., 1981[56]
Moguisteine	[(R,G)-2-(2-methoxyphenoxy)-methyl-3-ethoxycarbonyl-acetyl-1,3thiazolidine	Morita K and Kamei J, 2000[57]
Cilomilast	Phosphodiesterase Inhibitors	Lü et al., 2004[58]
NS1619	K^+ Channel Openers	Morita and Kamei, 2000[57]
Furosemide	Cl^- Pump Inhibitors	Foresi A, 1996[59]
Ouabain	Ouabain-Sensitive Na^+-K^+ ATPase Inhibitors	Gemmell W, 1890[60]
Montelukast	Leukotriene Receptor Antagonists	Kawai S et al 2008[61]; Wang K et al., 2014[62]
8-[Bis(2-chlorophenyl) methyl]-3-(2-pyrimidinyl)-8-azabicyclo[3.2.1.]octan-3-ol	Tropan Derivatives with High Affinity for the Nociceptin Opioid Receptor (Nociceptin)	McLeod et al., 2010[63]
Anandamide	Selective Cannabinoid 2 Receptor Agonists	Calignano et al., 2000[64]
SB-705498	Transient Receptor Potential Vanilloid 1 Receptor Antagonists	Rami et al., 2006[65]
Baclofen	GABA Receptor Agonists	Canning B.J. et al., 2012[66]
E121	Enaminone	El-Hashim et al., 2010[67]
Gabapentin	Gabapentin	Mintz S and Lee J.K. 2006[68]
Thalidomide	Immunomodulatory drug	Horton et al., 2008[69];2012[70]
Botulinum toxin A	Botulinum A Toxin	Chu et al., 2010[71]

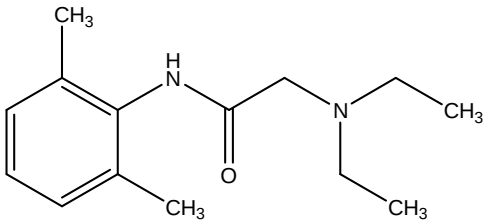
The structures of some currently used antitussive drugs are shown in the Figure-1



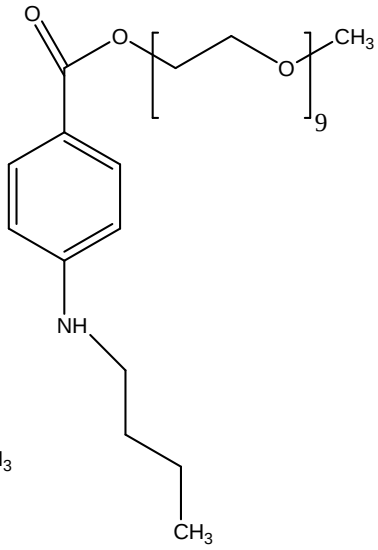
Dextromethorphan hydrobromide



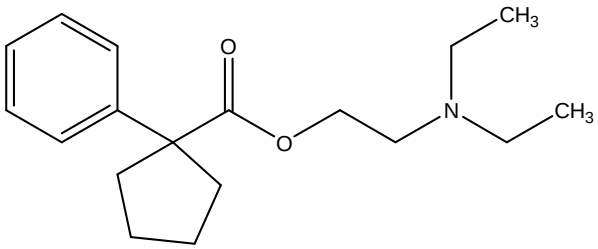
Codeine.



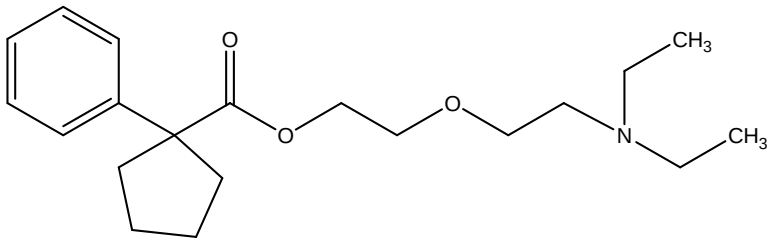
Lidocaine or Lignocaine.



Benzonatate

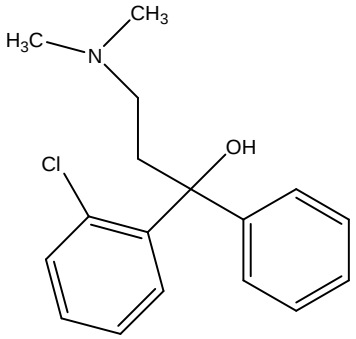


Caramiphen.

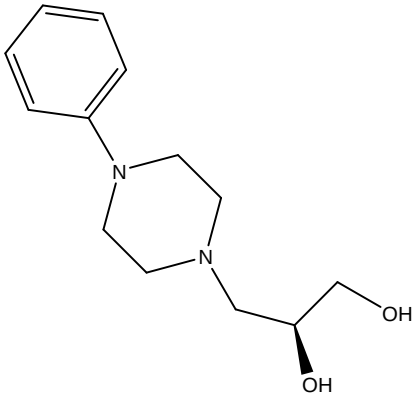


Carbetapentane.

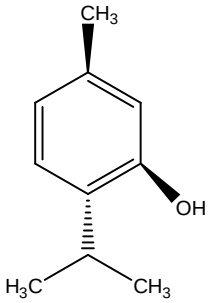
Figure-1: Structure of some currently available antitussive drugs (Continued)



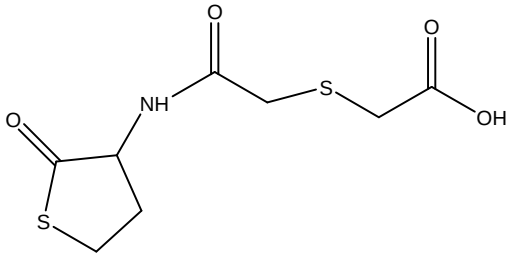
Chlophedianol



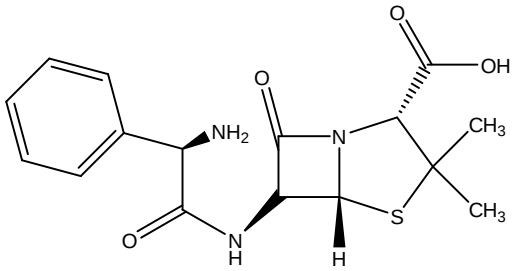
Levodropropizine



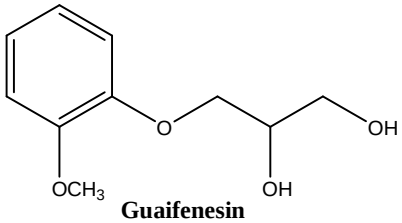
Menthol



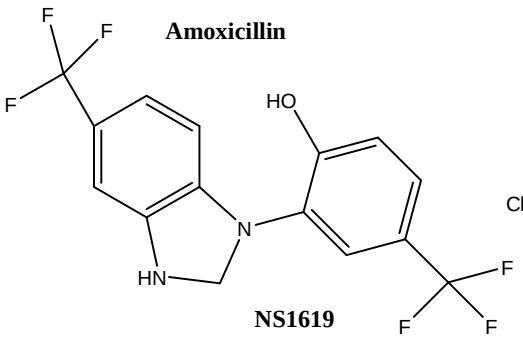
Erdosteine.



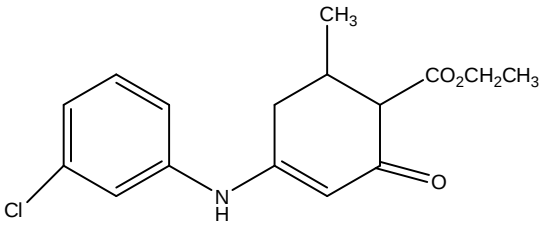
Amoxicillin



Guaifenesin

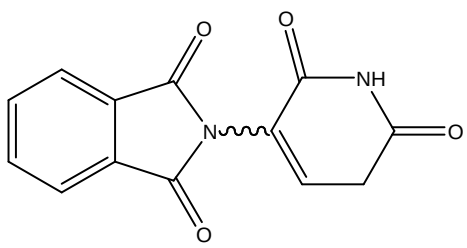


NS1619

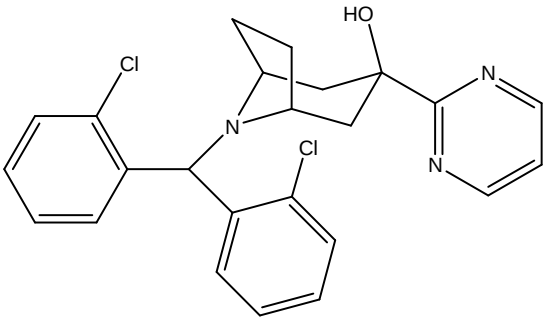


E121

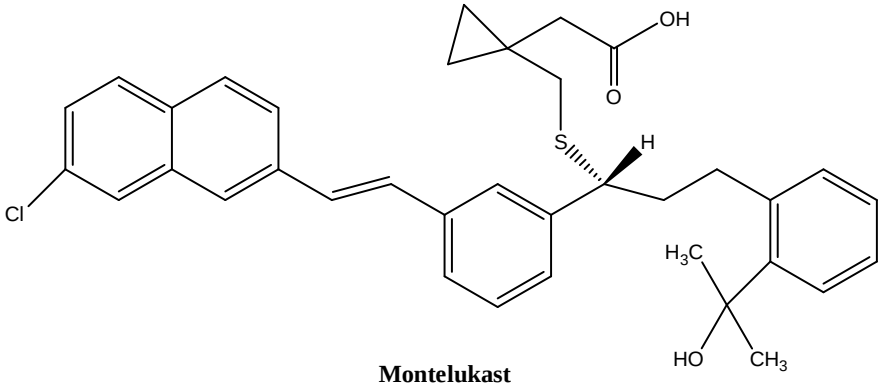
Figure-1-: Structure of some currently available antitussive drugs (Continued)



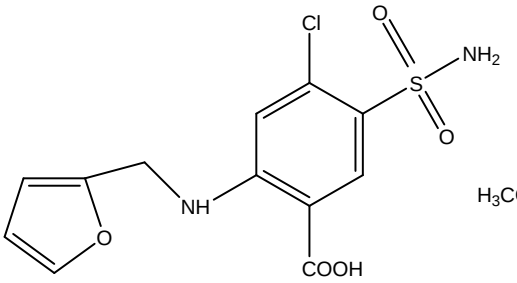
Thalidomide



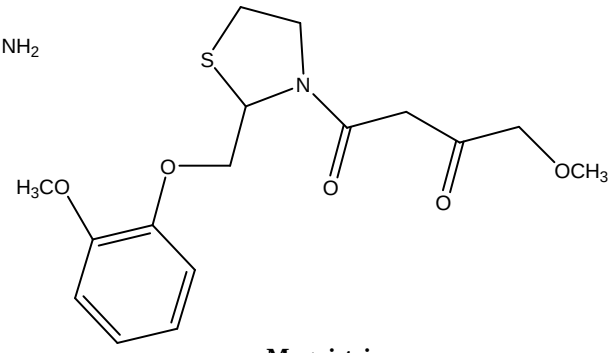
Tropan



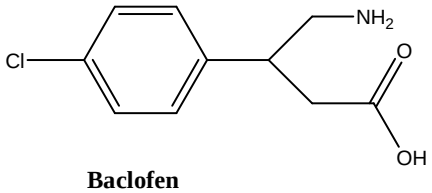
Montelukast



Furosemide.



Moguisteine



Baclofen

Figure-1-: Structure of some currently available antitussive drugs

Improvement of antitussives by model medical test

According to International Respiratory Societies the development of antitussive drugs depend on the high quality clinical trial. This high quality clinical trial includes patient selection, trial design, assessment of cough severity and the determination of sample size, the ideal trial. The assessment of cough severity includes Symptom scales, Quality of life, Cough reflex sensitivity, Cough monitoring. A randomized controlled design, utilizing both subjective and objective cough severity outcome parameters and paying attention to patient selection, sample size and choice of placebo are the important parameters of the ideal clinical trial[72].

Antitussive agents from nature: Herbal remedies for cough

The use of medicinal herbs for the alleviation of respiratory diseases like common cold, acute bronchitis, pneumonia, pertussis, flu is well documented. In this connection Phytotherapy uses botanical compounds which have exactly defined chemical composition and structure. Recent data showed that natural compounds such as polysaccharides, alkaloids, flavonoids, saponins, tannins, and terpenoids possessing anti-tussive and expectorant effects[73]. Nature produces plant made medications which is the supplement of the synthetic drugs and engineered protein, gene therapy. In these way natural products has a major contribution to the drug discovery and development process. Various victorious investigations on medicinal plants proved that nature is the promising supplier of new and semi-synthetic drugs[8,9]. According to Wang and Quinn, 2010[74] a large number carbohydrate polymers shows pharmacological activities through complex reaction cascades. Nosál'ová et al., 2006[73] reported that herbal polysaccharides also play an important role in the development of antitussive drugs.

Some common herbal antitussive herbs are *Acacia catechu* (L.f.) Willd. (Mimosaceae), *Acorus calamus L.* (Acoraceae), *Adhatoda vasica* Medic. (Acanthaceae), *Allium sativum* L. (Amaryllidaceae), *Angelica archangelica* L. (Apiaceae), *Astragalus membranaceus* (Fisch.) Bunge (Fabaceae), *Carum copticum* L. (Apiaceae), *Lavandula angustifolia* L. (Lamiaceae), *Lobelia inflata* L. (Campanulaceae), *Salvia officinalis* L. (Lamiaceae), *Sambucus nigra* L. (Caprifoliaceae), *Tussilago farfara* L. (Asteraceae), *Valeriana officinalis* L. (Valerianaceae), *Verbascum thapsus* L. (Scrophulariaceae), *Zingiber officinale Rosc.* (Zingiberaceae).

Herbal antitussives are broadly classified as centrally acting antitussives and peripherally acting antitussives. Centrally acting antitussives agents enhance the medullary cough center's threshold; e.g., poppy, *Papiver somniferum*; active chemical constituents are heroin, morphine, and codeine. These antitussive are supposed to work as cerebral sedatives through the liberation of endorphins. On the otherhand peripherally acting antitussives acts through bronchodilation. Mostly

used herbal bronchodilator is ma hunag, isolated from Ephedra herb, *Ephedra sinica*. The active phytochemical constituents are d-pseudoephedrine, l-ephedrine. These phytochemicals alleviate bronchospasm and mucosal congestion. Ephedra alkaloids, ma huang takes an important place in Traditional Chinese Medicine (TCM) for its both central and peripheral actions. It is extensively used for the treatment of respiratory tract disorders, including cough[75].

Indian herbal antitussive agents and expectorants

Extracts from the herbal products contain considerable amount of polysaccharides or their glycoconjugates which have a number of biological activities for instance antioxidant, anti-inflammatory, immunomodulating, bronchodilating, or antiallergic. For this reason herbal extracts possess cough suppression activity[76]. According to ˇSutovská et al., in 2007[77], the antitussive activity of the polysaccharide increases with the amount of uronic acid. This fact is supported by the works of Chayed and Winnik in 2007[78] who reports the significance of the ionic charge on antitussive activity. Besides this neutral polysaccharides like arabinose and galactose also show promising antitussive activities[79].

In Indian ayurvedic system Trikatu is extensively used coughs, colds, fevers, asthma, respiratory problems and also for improvement of the digestive disorders. Trikatu is prepared by the blend of Shunti (dry ginger), Maricha (black pepper), and Pippali (Indian long pepper). Although the said constituents show their distinctive fitness profit but when there are taken together their potency increases significantly[80]. A combination of protein-digesting (proteolytic) enzymes or proteases called bromelain is found in Pineapple (Ananas comosus (L.) Merr., Bromeliaceae). Bromelain possesses cough suppressing activity and is used as a remedy of sinusitis and allergy-based sinus issues. Honey can alleviate coughs more effectively than mostly used medicines Dextromethorphan. Jaggery (Canesugar of Saccharum officinarum L., family Poaceae) is used to soothe cough and congestion. Lemon (Citrus lemon (L.) Burm. F. , Rutaceae) fruits possesses the power of therapeutic coughs. The leaves and roots of the Marshmallow (*Althaea officinalis* L., family Malvaceae) herb have been used since prehistoric times for the treatment of sore throats and coughs. Onion (*Allium cepa L, Amaryllidaceae*) is also used for the treatment cough and sometimes it is used mixed with honey and comfrey tea for the ailment of dry cough. Menthol in peppermint (Mentha piperita L., Lamiaceae) acts as a decongestant by soothing the throat and serving to collapse mucus. The extracted materials from Thyme (*Thymus vulgaris* L., Lamiaceae) is used in the treatment of the respiratory diseases like coughing and short-term bronchitis. Actually the flavonoids present in the leaves which relax the throat muscles concerned in coughing and also lessen inflammation[81].

Table-3:- Some common and selected herbal antitussive agents

Serial No	Botanical Name (Family) and Common name	Parts used	Phytoconstituents	Medical use as antitussive agents	References
1	*Adhatodavasica* Medic. (Acanthaceae) Vasaka	Leaf, flowers, bark	Pyrroquinazoline alkaloids including vasicine, vasicol,vasinone and Arabinogalactan	Asthma, bronchitis, antitussive, cough, expectorant	Sultana et al., 2016[81]; Chattopadhyay et al ., 2011[11]
2	*Cinnamomumcamphora*(L.) Presl. (Lauraceae) Camphor	Essential oil	1,8-Cineole, α-terpinene, borneol, camphor, carvacrol, caryophyllene, citronellol, eugenol , geraniol, kaempferol, limonene, p-cymene , safrole, vanillin	Colds, coughs, bronchitis	Sultana et al., 2016[81]
3	*Eupatorium perfoliatum*L. (Asteraceae) Boneset	Aerial parts	Quercetin, kaempferol, rutin, eupatorin, terpenoidssesquiterpene lactones, volatile oil, resin	Bronchitis, colds, cough, flu, immunostimulant	Sultana et al., 2016[81]
4	*Lobelia inflata*L. (Campanulaceae) Lobelia	Aerial parts, dried flower, seed	Lobeline, isolobinine, lobelanidine, resin, fats, lobinaline, lobelacrin, labelianin, gum, chelidonic acid.	Addiction, asthma, bronchitis, cough, sore throat, stoppage of smoking	Sultana et al., 2016[81]
5	*Marrubiumvulgare*L. (Lamiaceae) Horn	Aerial part	Marrubiin (a bitter principle), diterpene alcohols (marrbiol, murrubenol), alkaloids, sesquiterpene, tannin, saponins, resin	Bronchitis, colds, cardiovascular, cough, sore throat	Sultana et al., 2016[81]
6	Melaleucaleucadendron L. (Myrtaceae) Cajeput Oil	Essential oil	Essential oil, α-terpineol, azulene, benzaldehyde, cajeputol, nerolidol, limonene	Colds, bronchitis, cough, congestion sore throat	Sultana et al., 2016[81]
7	*Ocimum sanctum L.* (Lamiaceae) Tulsi	Leaves, Essential oil	Ascorbic acid, β-carotene, β-sitosterol, carvacrol, tannin, eugenol, linoleic acid, methyl chavicol, oleic acid, palmitic acid, saponins, stearic acid,	Colds, cough, congestion, flu,	Sultana et al., 2016[81]

8	*Pelargonium sidoides*. DC. (Geraniaceae) Umckaloaba	Aerial part	Coumarin, 5,6-dimethoxy-7-hydroxy-coumarin	Acute bronchitis, tonsillopharyngitis (sore throat), common cold, sinusitis, cough.	Sultana et al., 2016[81]
9	*Prunusserotina* Ehrn. (Rosaceae) Whild Black cherry	Fruit, Bark	Acetylcholine, kaempferol, p-coumaric acid, prunasin, quercetin, scopoletin, tannins.	Bronchitis, colds, congestion, cough,	Sultana et al., 2016[81]
10	*Sambucusnigra* L. (Caprifoliaceae) Elder berry Flower,	Berries	Eessential oil, palmitic, linoleic and linolenic acids, triterpenes, flavonoids (flowers); pectin, sugar, vitamin C, flavonoids (berries); cyanogenic glycosides (leaves).	Bronchitis, colds, congestion, cough, , flu, sinus, sore throat	Sultana et al., 2016[81]

11	*Tussilagofarfara* L. (Asteraceae) Coughworth	Seeds, stem	Mucilage, alkaloid, saponins, tannin (especially in the leaf).	Asthma, bronchitis, colds, congestion, cough, smoking inhibitor	Sultana et al., 2016[81]
12	*Valerianaofficinalis*L. (Valerianaceae) Velerien root	Root	Acetic acid, ascorbic acid, β-ionone, caffeic acid, quercitin, valeric acid	Addiction, cardiovascular, cough, insomnia, stoppage of smoking	Sultana et al., 2016[81]
13	*Verbascum Thapsus* L. (Scrophulariaceae) Mullein	Flower, Leaves, Root	Verbathasin A, crocetin, hesperidin, ascorbic acid, coumarin, verbascoside	Congestion, cough, ear, sore throat, stoppage of smoking	Sultana et al., 2016[81]
14	*Veronica officinalis*L. (Plantagenaceae) Sleepwel	Flower part	Organic acids, sugars, flavonoids, resin and tannins.	Cough	Sultana et al., 2016[81]
15	*Zingiberofficinale* Roscoe (Zingiberaceae) Ginger	Rhizome	Zingiberone, bisabolene, Gingerols, shogaol, paradols, fats, protein, starch, vitamins, amino acids.	Cold, Coughs, Flu, Cardiovascular	Sultana et al., 2016[81]

MECHANISM OF ACTION

The drugs used for the pediatric cough treatment contains antitussive, decongestant, expectorant, antihistamine. The antihistamines include brompheniramine, chlorpheniramine, and diphenhydramine; the antitussive is dextromethorphan, the decongestant is phenylephrine, and the expectorant is guaifensin[82]. The currently available antitussive drugs are assumed to operate at the brainstem level and to influence numerous neuromediators concerned in cough[83-85]. According to Nosál'ová et al., 2013[19] the cough reflex modulation, initiated from the lower airways are done by esophagus, nose, or ear are known to modulate the cough reflex. Herbal treatment influences some of these said afferent inputs. The aqueous extracts of *Adhatoda vasica, Withania somnifera, Glycyrrhiza glabra, Psidium guajava, Piper nigrum, Nyctanthes arbor-tristis, Solanum virginianum, Andrographis paniculata* contains Arabinogalactan and arabinogalactan protein (AGP) i.e, polysaccharides which possess bioadhesive effects on the epithelial mucosa, defending the cells against local oral or pharyngealirritation. These said polysaccharides show their pharmacodynamic activity by the formation of their own layers on the airway mucous. In this manner the AGP exhibit coughs suppression activity by the indirect control of the sensitivity of the cough. The soothing mucosal effects of the said polysaccharides can be attributed to their lowering the sensitivity of the cough receptors and delays cough onset. These water soluble polysaccharides defend the mucous against physical, chemical, and microbiological irritants thorough the formation of bioadhesive gel layer. These polysaccharides influence epiphsryngeal nerve terminus by the promotion of salvation. Comparabale to saponins, polysaccharides enhance the emission of mucus through the vago-vagal reflex. Polysaccharides have the capacity to rehydrate the epithelium. In this way it reduces the dry cough supporting phlegm expectoration. Branched side chains of the arabinogalactans may be involved in the antitussive activity although glycosidic linkage patterns of galactose residues are not the contributors. All these aforesaid mechanisms playing a major role in the 'soothing' effects. Although the antitussive activity of the polysaccharide is not due to the bronchodilation. Exact mechanism of action is still unknown and more studies are needed to establish this[10-17, 86-88].

CONCLUSION

Recently used antitussives and expectorants such as opioids possess undesirable side effects like enhancement of the viscosity and elasticity of mucus, bronchoconstriction, respiratory depression. Mostly used antitussive drug codeine has some serious adverse effects such as cardiac arrhythmias, depressed consciousness and encephalopathy, hallucinations and deaths. For this reasons this drug is restricted to the children. Scientists and researchers are now searching for a novel, less toxic, more effective antitussive drug development. In this context herbal extractions from

medicinal plants containing polysaccharides, alkaloids, flavanoids are safe and less toxic, more effective than codeine. The arabinoglactans isolated from *Glycyrrhiza glabra*, *Adhatoda vasica, Withania somnifera* exert antitussive activitiy 81%, 67%, 61% respectively which is analogous to the the antitussive activity of codeine (62%). In this way herbal drugs and extractions taking a valuable place in the treatment of respiratory diseases and cough problems.

Nature generously supplies the novel antitussive agents from the ancient era. These herbal products can be used an alternative of opioid antitussives. This study gives the scientific basis on the use of natural products in the treatment of cough and also resolve the economic burden of the society due to the cost of medication as the natural products are easily available, cheap, non-toxic, wide acceptability.

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