Topical Review Article

Laūq: A Sustained-Release Dosage Form for Respiratory Disorders in Traditional Persian Medicine

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Hossein Karegar-Borzi, MD[1], Mehdi Salehi, MD[1], and Roja Rahimi, PharmD, PhD[2]

Abstract

Laūq is a pharmaceutical dosage form that had been mainly used for the treatment of various respiratory disorders in traditional Persian medicine. It is important from 2 aspects: a dosage form with efficient and optimum delivery of drugs to the respiratory tract and biological effects of its ingredients. Natural medicine in laūq has been demonstrated to act in respiratory disorders by their antitussive, antiallergic, anti-inflammatory, antioxidant, spasmolytic, and antibacterial activities. Some of these natural remedies act by most of the mentioned mechanisms such as *Cydonia oblonga*, *Glycyrrhiza glabra*, *Crocus sativus*, *Hyssopus officinalis*, *Foeniculum vulgare*, and honey. However, the evidence is limited including *Cassia fistula*, *Papaver somniferum*, and *Drimia maritima*. According to positive pharmacokinetic and pharmacodynamic aspects of laūqs, they may be considered as efficient dosage forms for delivery of drugs to the respiratory tract. For better compatibility of patients, it could be substituted laūqs with newer drug delivery systems like lozenges.

Keywords

laūq, respiratory disorders, natural medicines, traditional Persian medicine, medicinal plants, herbal medicine

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Laūq is a pharmaceutical dosage form that had been used mainly for the treatment of various respiratory disorders in traditional Persian medicine. It is a thick and sticky dosage form that was prepared by mixing powdered natural drug(s) with honey or sugar syrup and administered orally and recommended to be licked.[1,2] Laūq has been proposed as a first choice dosage form for treatment of respiratory disorders in traditional Persian medicine.[3,4]

In this review, indications and mechanisms of action of laūqs are described and then natural medicines that are used in formulation of laūqs and possible evidence of their efficacy in modern medicine are comprehensively reviewed. For this purpose, first traditional Persian medicine literatures were revised to derive these natural medicines; then electronic databases including PubMed, Scopus, and Google Scholar were searched for each of these medicines, and all retrieved articles were examined to obtain studies giving any in vitro, in vivo, or clinical evidence of their efficacy in the treatment of respiratory disorders.

Indications

Laūqs had not been specified to respiratory disorders and were formulated for other diseases like epilepsy, kidney inflammation, kidney stones, bladder stones, fever, premature ejaculation, reduced sperm count, hemorrhoid, intestinal ulcers, and colic[1]; but their main indication was for respiratory diseases. For example, from 80 Laūqs named in Canon of medicine about 60 (76%) are for the respiratory system.[3] Among respiratory disorders that laūqs were administered for, it could be implied to asthma, dyspnea, orthopnea, pleural pain, catarrh, productive and dry cough, pleurisy, hoarseness, pneumonia, hemoptysis, pharyngitis, laryngitis, and tuberculosis. Some respiratory laūq formulations derived from a famous traditional Persian pharmaceutical literature, *Gharabadin Kabir*, with their components and indications have been shown in Table 1.[1]

[1] Department of Traditional Medicine, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Traditional Pharmacy, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author:
Roja Rahimi, PharmD, PhD, Department of Traditional Medicine, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: rojarahimi@gmail.com

Table 1. Some Laūq Formulations in a Popular Traditional Persian Pharmaceutical Literature, *Gharabadin Kabir*.

Laūq's Traditional Name	Ingredients	Targeted Respiratory Disorder(s)
Laūq Squill	Squill, honey	Dyspnea, asthma, cough
Laūq Khashkhash	*Papaver somniferum* seeds, starch, *Astragalus tragacantha*, *Acacia Arabica*, *Cucurbita maxima* seeds, sugar, *Cydonia oblonga*, *Rosa damascene*	Catarrh
Laūq Banafsaj	*Viola odorata*, *Cassia fistula*, *Vitis vinfera*, *Cordia myxa*, sugar, *Amygdalus communis*	Cough
Laūq Teen	*Ficus carica*, *Echium amoenum*, *Zizyphus jujube*, *Cordia myxa*, *Viola odorata*, *Cassia fistula*, *Amygdalus communisl*	Cough dry
Laūq Khyar shanbar	*Cassia fistula*, *Astragalus tragacantha*, *Acacia arabica*, *Amygdalus communis*, *Faba vulgaris*, sugar	Pneumonia, pleurisy, hoarseness
Laūq Zoofa	*Hyssopus officinalis*, *Lilium candidum*, sugar	Dyspnea, asthma, chronic cough
Laūq Onnab	*Zizyphus jujuba*, *Althaea officinalis*, *Astragalus tragacantha*, *Vitis vinfera*, *Viola odorata*, *Glycyrrhiza glabra*, *Plantago ovata*, sugar	Fever, cough
Laūq Sepestan	*Cordia myxa*, *Vitis vinfera*, *Cassia fistula*, sugar	Cough pleurisy, asthma
Laūq Shyrin bayan	*Glycyrrhiza glabra*, *Astragalus tragacantha*, *Ferula galbaniflua*, *Amygdalus communis*, *Foeniculum vulgare*, honey	Cough chronic
Laūq Badam	*Amygdalus communis*, *Cucurbita maxima* seeds, *Acacia arabica*, *Astragalus tragacantha*, starch, *Glycyrrhiza glabra*, *Crocus sativus*, sugar, *Rosa damascene*	Cough, hoarseness

Mechanisms of action

As mentioned, laūq is a thick and sticky dosage form that should be used by licking. The physicochemical properties and method of administration increase the transit time of drug from esophagus and thus increase the absorption of drug to trachea. Moreover, it causes continuous and sustained release of drug to the respiratory tract.[2,5,6] Although the drug could be absorbed from stomach and reach the respiratory tract by blood circulation, its bioavailability markedly decreases. Moreover, it may be metabolized by liver enzymes and hence deactivated.[5,6]

Natural Medicines Used in the Formulation of Laūq

Honey

Honey has been used as a food and as a traditional medicine for about 6000 years[7]; apart from protection of drugs from spoilage,[8] honey has a significant antibacterial activity.[9] It has shown significant antibacterial activity against *Streptococcus faecalis*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* (Pneumococci).[10,11] The antibacterial activity of honey is due to its osmotic effect, acidity, production of hydrogen peroxide as a powerful antiseptic, the presence of nitric oxide end products, and immunostimulant properties by increasing lymphocytic and phagocytic activity and antibody production.[7,12]

When honey is taken, it acts topically on the upper respiratory tract, and after being absorbed into the blood, it acts on the lower respiratory tract.[10] The World Health Organization has recommended using honey as a potential treatment of cough.[14] Sweet substances inherently cause reflex salivation and also may cause the secretion of airway mucus and lead to a soothing effect on the larynx and pharynx, thus reducing cough (particularly dry cough). On the other hand, these secretions can improve mucociliary clearance via expectorant activity.[15] Honey also acts as a carrier for transporting of drugs to the respiratory tract.[13] Due to its inhibitory effects on prostaglandins, honey acts as a potent anti-inflammatory agent.[12] It also reduces edema in inflammatory tissues.[16] In addition, different antioxidant compounds such as vitamin C, flavonoids, monophenolics, and polyphenolics are present in honey that may be responsible for its beneficial respiratory effects.[17,18]

Hyssopus officinalis *L*

Flowering parts of *Hyssopus officinalis* have been used in the formulation of laūqs for the treatment of several respiratory diseases such as chronic cough, asthma, swelling of the lungs, and catarrh.[8] Methanolic extract of *H officinalis* exhibited potent antioxidant activities.[19] The essential oil showed antioxidant properties and antimicrobial activity against *Staphylococcus pyogenes* and *S aureus*.[20,21] Major compounds of *H officinalis* essential oil are pinocarvone, pinocamphone, β-pinene, isopinocamphone, terpinene-4-ol, carvacrole, and *p*-cymene.[20-22] *H officinalis* exhibited strong antifungal activity against several *Candida* species.[23] It demonstrated antiasthmatic activity in rats by increased secretion of IL-17 and balanced Th1/Th2 cytokines.[24] It also regulated the differentiation of Th1, Th2, and Th17 on transcription level.[25] Extracts of the leaves have mild spasmolytic activity.[26]

Crocus sativus *L*

Intraperitoneal injection of the ethanolic extract of *C sativus* and its main constituent, safranal, exhibited antitussive activity in guinea pigs.[27] *C sativus* showed a potent relaxant effect on tracheal chains of guinea-pigs that was comparable to or even higher than theophylline. It was demonstrated that safranal is responsible for this relaxant effect.[28] The aqueous-ethanolic extracts of this plant had a relatively potent stimulatory effect

on β-2-adrenoceptors[29] and an inhibitory effect at histamine 1 receptors.[30] The extract of *C sativus* significantly decreased tracheal responses, plasma levels of inflammatory mediators including interleukin-4, and total NO and nitrite but increased interferon-γ and interferon-γ/interleukin-4 ratio, on sensitized guinea pigs.[31] Also, *C sativus* and safranal exhibited a prophylactic effect on total and differential count of white blood cells in blood of sensitized guinea pigs comparable with that of dexamethasone. They prevented increase of eosinophil and lymphocyte counts but increased neutrophil count in sensitized guinea pigs. These results show the prophylactic effect of *C sativus* on inflammatory disorders such as asthma.[32] Methanol extract of *C sativus* (Greek saffron) exhibited high antioxidant activity that may be attributable to constituents like crocin and safranal. These 2 bioactive constituents showed high radical scavenging effect.[33]

Cassia fistula *L*

The leaves of *Cassia fistula* have been used in formulation of laūqs for the treatment of pneumonia, cough, and catarrh.[34] *C fistula* contains many components like saponin, triterpenoids, steroids, glycosides, anthraquinone, and flavonoids. Different extracts from *C fistula* showed remarkable antibacterial activities against 2 gram-positive (*Staphylococcus aureus* and *S pyogenes*) and a gram-negative (*Pseudomonas aeruginosa*) human pathogenic bacteria as compared with standard drugs.[35-37] The acetonic extract of flowers, leaves, and bark of this plant has been shown to be most active and have a more strong antibacterial activity than the corresponding methanolic and ethanolic extracts.[38] This plant has been explained to be beneficial against tuberculosis glands in the Indian literature.[35] The aqueous and methanolic extracts of its bark were found to possess remarkable anti-inflammatory effect in both acute and chronic models of inflammation in rats. This activity of the extracts may be due to inhibition of the mediators of inflammation such as histamine, serotonin, and prostaglandin.[39] The methanol extract of *C fistula* was reported to be effective on a cough induced by sulfur dioxide gas in mice comparable to that of codeine phosphate.[40]

Adiantum capillus-veneris *L*

Adiantum capillus-veneris has been used for the treatment of asthma in traditional Persian medicine.[41] Also, this plant has been used in Europe for the treatment of chronic pulmonary catarrh and other respiratory ailments such as cough.[42] The alcoholic extract of *A capillus-veneris* contains several compounds like triterpenoids (such as isoadiantone) and flavonoids (such as quercetin).[43] Water, ethanol, and methanol extracts of leaves, stems, and roots of *A capillus* showed significant antibacterial activity against most of the multidrug-resistant bacterial strains like *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.[44,45] Total alcoholic extract and its hexane fraction revealed significant anti-inflammatory activity in formalin-induced edema comparable with sodium salicylate. The anti-inflammatory activity of the total extract and its hexane fraction may be attributed to inhibition of inflammatory mediators such as histamine, 5HT, prostaglandins, and bradykinins. The flavonoids in total extract and sterols and triterpenes in hexane fraction may be responsible for these activities.[43]

Glycyrrhiza glabra *L*

Glycyrrhiza glabra has been used in formulation of laūqs for the treatment of asthma, dyspnea, cough, and hoarseness.[8] It helps remove congestion in the upper respiratory tract.[46] Also, it reduces muscle spasms and has mucolytic activity.[47]

Its major chemical constituents are glycyrrhizin, glycyrrhizic acid, liquilitin, liquiritigeninglabridin, hispaglabridins, glabrin, triterpene sterols, saponin, and isoflavones.[46,48] Studies indicated that *G glabra* Linn possesses antibacterial, antiviral, and anti–herpes simplex activity. Acetone extract of this plant showed significant antibacterial activities against 2 gram-positive (*Bacillus subtili* and *Staphylococcus aureus*) and a gram-negative (*Pseudomonas aeruginosa*) bacteria. Its antibacterial effect was better than streptomycin.[49] Saponins, alkaloids, and flavonoids derived from *G glabra* exhibited potent antibacterial and antioxidant activities.[46] Methanolic extract of *G glabra* has antituberculosis effect.[50] Immunomodulating effects of glycyrrhizin and glycyrrhetinic acid has been proven.[51] *G glabra* constituents showed anti-inflammatory activity due to inhibition of phospholipase A2, similar to the action of hydrocortisone. Glycyrrhizic acid inhibited cyclooxygenase activity and prostaglandin formation in vitro. Glycyrrhizin and glabridin inhibited the generation of reactive oxygen species by neutrophils at the site of inflammation.[50] Ethanol extract of *G glabra* exhibited obvious antitussive activity against chemically induced cough in mice comparable to codeine sulfate.[52] Liquiritin inhibited capsaicin-induced cough.[53] Liquilitin and liquiritigenin acted as peripheral and central antitussive agent. Glabridin is a remarkable antioxidant and ulcer-healing compound, which might be useful in minimizing the extent of ischemic damage to the tracheal and pharyngeal mucosa and accelerate their healing.[48] Preparations from *G glabra* have been used clinically as powerful antiallergic agents in Japan for the past 60 years.[51] It has been revealed that glycyrrhizic acid nasal drop is similar to the nasal spray of beclomethasone in the treatment of severe symptoms of allergic rhinitis (rhinorrhea, sneeze, congestion, and pruritus).[54] The root extract has exhibited an immunomodulating activity.[55]

Ficus carica *L*

Ficus carica is used in traditional Persian medicine for cough, violence throat, and used as an expectorant.[3] The methanol extract of *F carica* leaves exhibited strong antibacterial activity against oral bacteria like *Streptococcus gordonii*, *S anginosus*, and *Aggregatibacter*.[56,57] The ethyl acetate extract of *F carica* had inhibitory effect on the *Pseudomonas aeruginosa*.[58] The methanol extract from the leaves exhibited antituberculosis activity. The fruits possess high level of polyphenols, especially anthocyanins and flavonoids, and have demonstrated significant antioxidant capacity.[57] The hydroethanolic extract of

fruit has antispasmodic activity. This activity perhaps mediated through the activation of ATP-sensitive potassium channel along with antiplatelet effect.[59]

Papaver somniferum *L*

The seeds of *P somniferum* have been used for treatment of asthma, catarrh, and cough.[8] Several valuable benzylisoquinoline alkaloids have been identified in *P somniferum*, such as narcotic analgesics (morphine and codeine), the muscle relaxant papaverine, and the antitussive drug noscapine.[60] Noscapine has suppressed cough by blocking the effect of bradykinin receptor activation in the airways.[61] *P somniferum* also showed antibacterial activity against several bacteria such as *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Staphylococcus aureus.*[62]

Althaea officinalis *L*

Althaea officinalis has been widely used for the treatment of the pneumonia, hemoptysis, cough, and catarrh in traditional Persian medicine.[8] It contains many constituents such as pectins, starch, mucilage, flavonoids (hypolaetin-8-glucoside, isoquercitrin, etc), scopoletin, and tannins. The studies showed that *A officinalis* possessed antimicrobial, antitussive, anti-inflammatory, demulcent, and many other pharmacological effects. A methanolic extract from root has been shown to have antibacterial activity against pathogens resident in the oral cavity (*Actinomyces odontolyticus*, *Fusobacterium nucleatum*)[63] and against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[64] In addition, hexane extract has shown antimicrobial activity against gram-positive and gram-negative bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus*) and antifungal activity against several fungi such as *Candida albicans*.[65] The hydroalcoholic extract of this plant also demonstrated bacteriostatic effect on *Pseudomonas aeruginosa*, *Staphylococcus aureus* and bactericidal effect on *Staphylococcus aureus*.[66] The root extract and isolated mucilage polysaccharide significantly reduced the intensity and the number of cough efforts from laryngopharyngeal and tracheobronchial areas in unanesthetized cats. These polysaccharides exhibited statistically significant cough-suppressing activity higher than that of the nonnarcotic drug used in clinical practice to treat coughing.[63] Rhamnogalacturonan, one of the constituents from mucilage, significantly reduced the number of cough efforts and intensity of attacks from the irritated laryngopharyngeal and tracheobronchial mucous membranes of the airways and promoted expectoration.[67] Also, it has shown marked antitussive effect in experimentally induced airways allergic inflammation.[68] Aqueous extract stimulated phagocytosis and release of leukotrienes and oxygen radicals from human neutrophils in vitro. In addition, it induced the release of interleukin-6, cytokines, and tumor necrosis factor from human monocytes.[69] Polysaccharides from root acted as a soothing agent by moderate adhesion to epithelial tissue of porcine buccal membranes.[63]

Cydonia oblonga *Mill*

Cydonia oblonga has been used in traditional Persian medicine for the treatment of asthma, orthopnea, and hemoptysis.[3] Phenolic extract of leaf contains kaempferol-3-O-glucoside and kaempferol-3-O-rutinoside.[70] The seeds possessed tannins, glycosides, and phenolic compounds. Ethanolic extract of *Cydonia oblonga* seeds had potential antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumonia.*[71] The methanolic extracts of pulp, peel, and seed have shown free radical scavenging activity much higher than standard antioxidant. Quercetin and quercetin-3-O-rutinoside were the most active antioxidants.[70,72] Hot water extract of fruit demonstrated antiallergic activity and had an inhibitory effect on a broad range of late-phase immune reactions of mast cells.[73,74] The extract relaxed carbamylcholine and K^+-induced contractions of isolated rabbit trachea, similar to verapamil.[75]

Rosa damascena *Mill*

Rosa damascena has been used for the treatment of hemoptysis, hoarseness, and catarrh in traditional Persian medicine.[41] It is a medicinal plant with several pharmacological properties such as antibacterial, anti-inflammatory, antioxidant, and antitussive effect. Antibacterial activity of *R damascena* was demonstrated against respiratory pathogens such as *Pseudomonas aeruginosa*, *Bacillus cereus*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis*,[76] and *Staphylococcus aureus.*[77] Antibacterial activity of essential oil was also shown against *Staphylococcus aureus* and *Pseudomonas aeruginosa.*[78,79] The more potent relaxant effect has been observed from ethyl acetate fraction of ethanolic extract and essential oil has been shown to be the most potent relaxant effect compared to other fractions on tracheal smooth muscle. Its effect was comparable with theophylline.[80] The mechanism(s) of relaxant effect of *R damascena* on tracheal may be produced by several mechanisms including stimulation of β-adrenoceptors, blocking effect on histamine (H1) receptors, muscarinic antagonistic effect,[81] and an inhibitory effect on calcium channels of tracheal chain.[78,81] The aqueous and ethanolic extracts of *R damascena* significantly reduced the number of coughs induced by citric acid in guinea pigs. The antitussive effect of this plant was comparable to codeine.[82] Decoction of the root of this plant was used by North American Indian tribes for treatment of children's cough.[83] *R damascena* has also demonstrated anti-inflammatory activity. Essential oil and hydroalcoholic extract inhibited carrageenan-induced rat paw edema. Furthermore, this plant contains ascorbic acid, which has antioxidant and anti-inflammatory effects.[78]

Drimia maritima *(L) Stearn*

Drimia maritima (squill bulb) is one of the best medicinal plants for treatment of many diseases, especially respiratory disorders in traditional Persian medicine. It also was used by herbalists for the treatment of pneumonia, chronic

Table 2. Mode of Action of Medicinal Plants Used in Laūqs Formulated for Respiratory Disorder.

	Activities							
Natural Medicines	Antibacterial	Spasmolytic	Antioxidant	Anti-inflammatory	Antiallergic	Antitussive	Radical Scavenging	References
Adiantum capillus-veneris	*			*				42-45
Althaea officinalis	*			*	*	*		63-69
Cassia fistula	*			*		*		35-40
Crocus sativus		*	*	*		*	*	27-33
Cydonia oblonga	*	*	*	*	*	*	*	70-75
Ficus carica	*	*	*					56-59
Foeniculum vulgare	*	*	*	*	*			91-97
Glycyrrhiza glabra	*		*	*	*	*	*	46-55
Honey	*		*	*		*		9-18
Hyssopus officinalis	*	*	*	*			*	19-26
Papaver somniferum	*					*		60-62
Rosa damascena	*	*	*	*		*		76-83
Drimia maritima			*				*	84, 85, 89, 90

bronchitis, asthma, cough,[84] and used as a cough syrup[85] for more than 2000 years.[86] Gee's linctus (old cough mixture formulation) is a pharmacy-only cough mixture available without prescription all over New Zealand. It contains squill, morphine, and ethanol. Squill in Gee's linctus is thought to act as an expectorant.[87] The vinegar and oxymel of squill lessened the constriction of air passages and acted like an expectorant agent.[88] Many compounds have been isolated from *D maritima*, such as scillaren, scillirubroside, scillarenin, and bufadienolide glycosides.[89] *D maritima* extracts are highly effective in the treatment of non–small cell lung cancer. The bulb extract was found to be more effective than conventional drugs of non–small cell lung cancer, cisplatin and gemcitabine ($P < .001$ and $P = .097$, respectively). The methanol extract showed better efficacy than the aqueous extract.[85] Various extracts especially ethanol extract from bulb have been shown significant antioxidant activity.[90]

Foeniculum vulgare *Mill*

The essential oil from *Foeniculum vulgare* possesses antibacterial effect against gram-negative (*Acinetobacter baumannii*, *Pseudomonas aeruginosa*) and gram-positive (*Staphylococcus aureus*, *Bacillus subtilis)* bacteria.[91] Jazani et al proposed the potential use of the *F vulgare* essential oil for the control of multidrug resistant *Acinetobacter baumannii* infections.[92] Oral administration of *F vulgare* fruit methanolic extract exhibited inhibitory effects against acute and subacute inflammatory disorders and type IV allergic reactions (anti-inflammatory activity). In addition, it significantly increased the plasma superoxide dismutase and catalase activities.[93] The aqueous extract of fennel exhibited a remarkable NO scavenging activity. The result suggests that *F vulgare* might be potent and novel therapeutic agents for the regulation of pathological conditions caused by excessive generation of NO.[94] Ethanol extract and essential oil from *F vulgare* exhibited relaxant (bronchodilatory) effects on isolated guinea pig tracheal chains.[95] The potassium channel opening effect of this plant may be responsible for this activity.[96] Moreover, the structural similarity of anethole (the main constituent of *F vulgare* essential oil) appears to be responsible for the various sympathomimetic activity of *F vulgare* such as bronchodilatory effect.[97]

Discussion

Laūq as a sustained-release dosage form for respiratory disorders in medieval Persia seems to have considerable pharmacokinetic and pharmacodynamic properties. The dosage form and method of administration have facilitated efficient and optimum delivery of drugs to the respiratory tract. Moreover, novel studies confirm positive biological activities of natural remedies used in formulation of laūqs. These natural remedies have been shown their efficacy in respiratory disorders by several mechanisms of action including antitussive, antiallergic, anti-inflammatory (via inhibitory effects on cytokines, prostaglandins, and leukotriens), antioxidant, spasmolytic, and antibacterial activities (Table 2). As shown in Table 2, some of these natural remedies act by most of these mechanisms, such as *Cydonia oblonga*, *Glycyrrhiza glabra*, *Crocus sativus*, *Hyssopus officinalis*, *Rosa damascene*, *Foeniculum vulgare*, honey, and *Althaea officinalis*. However, some act with only 2 or 3 mechanisms including *Ficus carica*, *Cassia fistula*, *Papaver somniferum*, *Drimia maritima*, and *Adiantum capillus-veneris*.

Apart from the above-mentioned drugs, there are several natural medicines in formulation of laūqs that have not been evaluated in respiratory disorders and their mechanisms of action are still unknown. Among them, it could be implied to *Amygdalus communis*, *Viola odorata*, *Acacia arabica*, *Punica granatum*, *Cordia myxa*, *Ziziphus jujuba*, *Echium Amoenum*, and *Polyporus officinalis.*

Among the novel dosage forms, linctuses and lozenges are similar to laūqs, maybe lozenges are the most similar dosage forms to laūqs. Thus, the formulation of laūqs could be used for designing lozenges as efficient dosage forms for respiratory disorders such as cough, asthma, sore throat, bronchitis, and so on.

Author Contributions

RR designed the study and edited the article. HK and MS collected data and wrote the article.

Declaration of Conflicting Interests

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Ethical Approval

This study is exempt from oversight by human subjects research protection as there were no human subjects involved.

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