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Review Article (Pages: 15205-15226)

Herbal Treatments for Asthma, according to Avicenna

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Abstract

Background: Conventional therapies using herbal medicine to treat asthma are employed by practitioners in Iran. The use of herbal medicine for asthma is rooted in traditional knowledge. Scientific evaluation of these historical documents could be valuable to find new potential applications in conventional medicine. Traditional Persian Medicine (TPM), which is widely known with the manuscripts of Avicenna and Rhazes, is one of the most ancient medical sets of beliefs.

Methods: In this study, firstly we introduce a series of medicinal plants that would be enormously valuable for treating asthma on the basis of Avicenna (The Canon of Medicine by Avicenna). After that, we review medicinal plants properties found in the pharmacological studies from electronic databases and then discuss their mechanism of action in asthma.for a detailed review, relevant abstracts and articles related to the above-mentioned areas were selected, including review articles on the subjects, along with clinical trial studies on animals and humans.

Results: The physicians of ancient Iran such as Avicenna treated asthma patients with a variety of medicinal herbs including Hyssop, Galangal, Zataria, Myrrh, Turpeth, Aristolochia, Cinnamon, Saffron, Ginger, Fennel and Anise. Some of these herbs are currently used, while others have the potential to be used in the future of asthma management. Various activities such as anti-inflammatory, bronchodilator, antitussive and etc. have been proposed by scientific studies on traditionally applied antiasthma plants.

Conclusions: According to the reviewed studies the Hyssop, Saffron, Ginger, Anise and Fennel have the highest pharmacological effects and role in the treatment of asthma. The effectiveness of the investigated plants is, further, confirmed in recent medical studies; therefore, different components of these herbs can be investigated for being utilized in manufacturing new drugs.

Key Words: Canon of Medicine, Ibn Sina, Iranian Traditional Medicine, Medicinal plant, Reactive airway disease.

* Please cite this article as: Sadr S, Kaveh N, Agin K, Choopani R, Kaveh S, Tahermohammadi H. Herbal Treatments for Asthma, according to Avicenna. Int J Pediatr 2022; 10 (1):15205-15226. DOI: **10.22038/IJP.2021.58082.4553**

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Received date: Aug.31,2021; Accepted date:Oct.12,2021

1- INTRODUCTION

Asthma is one of the major causes of chronic airway disease that has affected 300 million people around the world (1). The incidence of asthma is increasing daily with the increase in pollution, stress and strain of life (2, 3). The pathology of asthma includes mucus glands hypertrophy, airways inflammation and bronchoconstriction (5, 6). The treatment of asthma has improved due to the widespread use of management guidelines along with the new findings regarding the mechanisms involved in asthma. (7). Currently, the management of asthma focuses on controlling the inflammatory process and patient's comfort (5, 8). Inhalational corticosteroids and β_2-agonists are known as the treatment of choice for asthma. These medications control inflammation and bronchial constriction (7). However, the ongoing efforts to discover a secure and efficient treatment for asthma prove that finding a drug with no local or systemic side effects is very difficult (2, 5). On the other hand, the prolonged course of the disease and the lack of preventive and therapeutic measures have encouraged asthma patients to try Complementary and Alternative Medicine (CAM). Patients living in developed countries have a better opportunity to use traditional medicine as either an exclusive or complementary therapeutic plan (9). Research conducted by the National Asthma Campaign discovered that 70% of asthmatic patients with severe disease and 60% of those with moderate disease had tried CAM. Herbal medicine is considered the third most common type of CAM used by both adult (11%) and pediatric (6%) asthmatic patients (10, 11). Traditional Persian Medicine (TPM) is also considered a type of CAM. TPM has a particular classification and management strategy for asthma. In this article we aimed to introduce the most famous effective herbs including Hyssop, Galangal, Zataria, Myrrh, Turpeth, Aristolochia, Cinnamon, Saffron, Ginger, Fennel and Anise in the treatment of asthma based on the reports by Avicenna, the great Iranian physician, and the recent studies.

2- METHODS

This study was a literature research Qanoon fi al-teb (The Canon of Medicine) the major reference of TPM written by Avicenna in 1025 CE. This book is determined as an Iranian traditional reference in medicine and pharmacy and is now used as reference for the Iranian PhD programs in traditional pharmacy. Two words of ‘‘zigho-al-nafas’’ and ‘‘rabv’’were searched in the above-mentioned book. Then the medicinal plants that Avicenna used in treating asthma were identified. In order to link traditional data with new findings, a search was performed on the pharmacological effects of the mentioned medicinal plants in Pub-Med and Google Scholar databases. Scientific names of the plants as well as their families were written according to www.theplantlist.org.

3- RESULTS AND DISCUSSION

Avicenna discussed the disease under the names of "Rabv" and "Zigh-ol-nafas" in the second volume of the canon of medicine, under the chapter of lung ailments. He mentioned various types and several etiologies for the disease. A type of the disease which results from accumulation of thick and sticky phlegm or "Balgham" humor in the airways is called "Rabve balghami". This disease is similar to asthma in definition and symptoms. It seems that asthma can be considered as a subset of "Rabve balghami". Avicenna believed that "Rabve balghami" is a chronic condition with episodes of remission and exacerbation, in which the respiratory rate of the patient increases, similar to the respiration of someone who is tired or has been running, along with symptoms including cough,

wheezing and dyspnea. Besides the treatment of "Rabve balghami", Avicenna focused on lifestyle factors including food and drinks, alertness and sleep, exercise and rest, excretion of body wastes, living environment and psychological factors. He also introduced a number of therapeutic approaches including enema, application of an ointment, single or compound herbal formulas which were tailored according to patient's symptoms, temperament, age, sex, occupation and geographic place. Avicenna mentioned phlegm or "Balgham" as well as cold and moist temperament, as the causes of "Rabve balghami". Therefore, remedies to treat this condition should be of warm and dry temperament (12).

In this assay we mentioned a small number of single herbs which Avicenna has recommended for "Rabve balghami" management as well as their effects based on recent studies. These herbs include: Hyssop, Galangal, Zataria, Myrrh, Turpeth, Aristolochia, Cinnamon, Saffron, Ginger, Fennel and Anise (**Table 1**).

3-1. Hyssop

Hyssopus officinalis L. (Lamiaceae) is a very common herb, especially in the East Mediterranean areas of central Asia. Hyssop possesses warm and dry properties. Its vernacular name in Iran is "Zoofa" (13). Hyssop contains various constituents including polyphenolic compounds mainly flavonoids apigenin, quercetin, diosmin, luteolin and their glucosides plus phenolic compounds like chlorogenic, protocatechuic, ferulic, syringic, p-hydroxybenzoic and caffeic acids (14). Hyssop is a popular herb in TPM that is recommended in catarrh, pneumonia, cough, asthma, and other inflammatory respiratory conditions (13). Studies indicate that Hyssop has anti-inflammatory and antioxidant effects, as well as antimicrobial (15). Hyssop can play an anti-inflammatory role by correcting the imbalance between Th1/Th2 cytokines and inhibiting the secretion of IL-17 (17, 18). Hyssop can regulate the secretion of interleukin (IL-4, IL-17) and interferon-γ (IFN-γ) (19). Hyssop reduces the inflammatory response of asthma by inhibiting the secretion of Eotaxin-2 (20). Hyssop corrects imbalance in MMP-9/TIMP-1 ratio and thus inhibits airway remodeling (21). The toxicological investigations showed that the LD50 for Hyssop was 99.5 µL/L on C. quinquefasciatus larvae (22).

3-2. Galangal

Alpinia galanga (L.) Willd. (Zingiberaceae) possesses warm and dry properties. This valuable plant is known as "Khulenjan" in Iran (13). Galangal contains a range of flavonoid compounds and volatile oils. Some of the flavonoids that exist in the rhizome of the plant include kaempferol, kaempferide, galangin, alpinin and quercetin. 1'-acetoxyeugenoi acetate and 1'-acetoxychavicol acetate (ACA) are present in the fruits of Galangal. (23). Galangal is traditionally used for a wide range of conditions including catarrh, asthma, chronic cough, and other respiratory problems (13).

A component of Galangal, ACA, was found to reduce the eosinophilic infiltration and the IgE level in the lungs of mice subjected to Ovalbumin (OVA). Furthermore, ACA can suppress airway remodeling, goblet-cell hyperplasia, and glycoprotein secretion. ACA can also inhibit the expression of Th2 cytokines, including IL-4, IL-13 and Th1 cytokines, including IL-12α and IFN-γ. Since immunologic and inflammatory reactions play the main role in asthma. ACA seems to be a suitable candidate for the management of asthma (25). A study reported that ACA increased cell apoptosis and had potential antioxidant activity; and could, therefore, reduce cytokine production by Th cells. (26). Toxicological investigations have shown that LD_{50} for

Galangal was 3,456 mg/kg on C. gestroi and C. curvignathus (27).

3-3. Zataria

Zataria multiflora Boiss is a thyme-like plant from the Lamiaceae family, which grows in the region of Iran, Pakistan and Afghanistan. Zataria possesses warm and dry properties. It is known in Iran by the name of "Avishan-e-Shirazi" (Shirazi thyme) (13). Zataria oil contains high amounts of thymol and carvacrol and thus displays strong anti-microbial activities (28). Also, Zataria and its constituent, carvacrol, have properties of anti-inflammatory and anti-chronic obstructive pulmonary diseases (COPD) (29). Zataria is traditionally used for a wide range of conditions including catarrh, asthma, chronic cough, and other respiratory problems. Also Zataria had an important role in TPM (28). Zataria extract has a protective role against tracheal hypersensitivity and can decrease the serum level of histamine, nitrite and nitric oxide (NO) and can improve asthma in sensitized guinea pigs (30). Information from in vitro and in vivo studies show that Zataria extract can increase IFN-γ, decrease IL-4, and improve the IFN-γ to IL-4 ratio (Th_1/Th_2 balance). Consequently, Zataria extract can be useful in reducing inflammations due to Th_1/Th_2 imbalance including asthma, allergy, autoimmune and infectious diseases (31). Zataria and its constituent carvacrol have a preventive therapeutic potential on lung inflammation and oxidative stress in COPD (29). Toxicological studies showed that carvacrol, the main constituents of Zataria, could cause 100% mortality at 10 µL/L air on Callosobruchus maculatus (32). A Study by Alavinezhad showed that Zataria and carvacrol, reduced wheezing and plasma level of plasma nitrite (NO^{2-}) and improved FEV_1% in asthmatic patients [1]. Another study by Boskabady et al. indicated that Zataria has a long-acting bronchodilatory effect in asthmatic patients in comparison to the xz theophylline effect [2].

3-4. Myrrh

Commiphora myrrha (Nees) Engl. (Burseraceae), a native of Northeastern Africa, Arabia (South West Asia), and India is a yellow aromatic resin obtained from scratching the bark of Commiphora genus. Myrrh possesses warm and dry qualities. It is known in Iran by the name of "Murr" (13). Myrrh resin extract is composed of phytochemicals such as terpenoids, steroids, flavonoids, alkaloids, tannins, glycosides, saponins, carbohydrates, along with aliphatic alcohol derivatives. TPM considers many therapeutic effects for Myrrh especially in problems such as asthma (33). Data gathered from recent studies show Myrrh to have antimicrobial (34) and anti-inflammatory (35) effects. It has been also used for inflammation and congestion of the lungs, cough, colds and asthma (35). Myrrh showed no toxicity on Swiss albino mice at 550 mg/kg (36).

3-5. Turpeth

Ipomoea turpethum R. Brown (Convolvulaceae), is a climbing perennial herb with branched roots called Turpeth which mainly grows in Iran, Bangladesh, India, Ceylon, Mauritania, Philippines, Africa and Australia. It is known in Iran by the name of "Torbod". Turpeth possesses warm and dry qualities (13). It comprises glycosidic resin, coumarins, β-sitosterol, and essential oils (37). Traditionally, its root has expectorant effect and can be used in a range of conditions such as bronchitis, cough, asthma and inflammations (38). Turpeth based on recent studies possesses antioxidant (39), bronchodilator (40), and antibacterial (41) qualities. The crude extract of Turpeth can be used in the treatment of asthma by antispasmodic and bronchodilator properties that are mediated through the presence of Ca^{2+} antagonist (40).

3-6. Aristolochia

Aristolochia clematitis L. (Aristolochiaceae), also known as Birthwort, grows mainly in North Africa, Europe and Asia. Aristolochia possesses warm and dry qualities. In Iran it is known by the name of "Zaravand" (13). The major constituents of Birthwort are aristolochic acids, aristolactam N-ß-D-glucoside, aristolone, ferulic acids and 4-coumaric acid. The diethyl ether, methanol and water extracts include flavonoids, free alkaloids, alkaloid salts, saponins, steroids, terpenoids, tannins, coumarins, reducing sugars, fatty acids and volatile oils (42).. New investigations on Birthwort indicate that it has anti-inflammatory, antioxidant (42) and antibacterial (43) effects. Birthwort has been used traditionally for a range of conditions such as bronchitis, pneumonia, and fever (42) A recent investigation shows that aristolochic acids and aristolactam can inhibit IL-6 and tumor necrosis factor (TNF)-α that are key regulators of inflammation and are implicated in several diseases. This study indicates that Birthwort has anti-inflammatory effects (44). The toxicological investigations showed LD_{50} 6.9 μL/mL on human kidney (HK-2) cells (45).

3-7. Cinnamon

Cinnamomum verum J. Presl. (Lauraceae) is commonly known as Cinnamon. This wooden tree belongs to tropical Asia and Africa. In terms of temperament Cinnamon is considered to be warm and dry. In Iran it is called "Darchini" (13) and is used as a medicine or spice. The essential oils and main components of Cinnamon include cinnamaldehyde, eugenol and guaiene (46). One study indicated that Cinnamon water extract (CWE) with anti-inflammatory properties can reduce lipopolysaccharide (LPS)-induced TNF-α in serum, so can be useful in the treatment of asthma (48). The toxicity studies suggest that the Cinnamon aqueous extract has low to moderate toxicity and the dosage less than 0.5 g/kg is confirmed to be safe in rats (49).

3-8. Saffron

Crocus sativus L. (Iridaceae), also known as Saffron, is a flowering plant. Saffron grows mainly in Iran as well as Greece and India. It is known in Iran by the name of "Zaffaran " and is both used as medicine and condiment. Saffron possesses warm and dry qualities. Saffron has been used for asthma (13). Characteristic components of Saffron are safranal, picrocrocin, and crocin (50). From a pharmacological point of view Saffron constituents have shown anti-tussive (51) and anti-inflammatory (52) activities. More recent investigations show that Saffron extract can reduce the number of inflammatory cells, white blood cells (WBCs) including eosinophils and platelets in the blood which may indicate its prophylactic effect on asthma (52, 53). Safranal can reduce the hyper-responsiveness of the airways as well as NO inducible nitric oxide synthase (iNOS) production, apoptosis of the bronchial epithelial cells and the production of Th2 type cytokine in the lungs (54). One study showed that Safranal has a relaxant effect on guinea pig tracheal smooth muscle, although this effect is less than that in theophylline users in the compared group (55). Long term oral administration of Saffron (56) and safranal (57) also decrease tracheal responsiveness in sensitized guinea pigs with methacholine. The ethanolic extract of Saffron and safranal has antitussive effects, due to its relaxant effect on airway smooth muscles (51). One study showed that hydroalcoholic extract of saffron could be effective in decreasing pulmonary inflammatory cells such as eosinophils in lung lavage of ovalbumin sensitized rats [3]. Another study by Zilaee M. et al. showed that capsules of saffron (100 mg/d) for 8 weeks have improving effects on

symptoms of patients with mild and moderate persistent allergic asthma [4].

According to LD_{50} values, safranal was low-toxic in acute intraperitoneal route and practically non-toxic in acute oral administration in both mice and rats (LD_{50} 4120±556 mg/kg) (58).

3-9. Ginger

Zingiber officinale Roscoe (Zingiberaceae), is one of the most popular spices throughout the world. First originated in south-east Asia, Ginger is now used worldwide to give the food a pleasant flavor. Ginger possesses warm and dry qualities. In Iran it is known as “Zangabil" (13). Ginger constituents can be divided into volatile and non-volatile groups. Volatile group includes sesquiterpene and monoterpenoid hydrocarbons which are responsible for the aroma and taste of Ginger. Non-volatile group includes gingerols, shogaols, paradols, and zingerone which give Ginger its pungent quality (59). The effect of Ginger on respiratory airways has been investigated in 3 studies using crude Ginger extract. The results showed its bronchodilator activity, inhibition of acetylcholine (ACE)-induced contraction and Ca^{2+} transients in guinea pigs (60). A study showed the ability of Ginger to prevent phthalate ester-associated asthma (61). Another one confirmed the anti-inflammatory effect of Ginger in respiratory infections (62). Besides, two other studies indicated that Ginger suppressed Th2-mediated immune responses and could play a role in the management of allergic asthma (63, 64). Yet another study revealed that Ginger could reduce the pulmonary damage due to the inflammation and hypoxia [5].

3-10. Fennel

Foeniculum vulgare Mill. (Apiaceae), known as Fennel is an annual or perennial aromatic plant originally from Asia, Southern Europe and Mediterranean region although today it is grown in other temperates and tropical regions of the world. In Iran it is known as “Razianeh” or “Badian”. Fennel possesses warm and dry qualities (13). The major constituents of Fennel are trans-anethole, estragole, fenchone, limonene, sesquiterpenoids, coumarins and polyphenolics (65). Fennel’s fruits are used as a spice for cooking in many countries while other parts such as the bulb, young shoots and leaves are useful household medicines. Fennel tea made from the seed is a popular medicine used in a range of conditions such as bronchitis and chronic cough (66). From a pharmacological point of view, *in vitro* and *in vivo* experiments have suggested the antibacterial (67), antioxidant (68) and anti-inflammatory (69) properties of Fennel. Recent investigations also suggest that the ethanol extract and essential oil of Fennel have bronchodilator and antibacterial activities (70, 71). Moreover, the oil of Fennel fruit can possibly control the house dust mite and reduce asthma (72). Study by Zhang S. et al. showed that trans-anethole as the main constituent of fennel acts as an anti-inflammatory constituent, influencing the regulation of Th17/Treg [6].

3-11. Anise

Pimpinella anisum L. (Apiaceae), commonly known as Anise, grows extensively in Asia, Africa and Europe. Anise seed possesses warm and dry qualities. In Iran it is known by the name of “Anisoon” (13). The major constituents of the seed are anethole, pseudo isoeugenol, coumarins, scopoletin, umbelliferone, estrols, terpene hydrocarbons, polyenes and polyacetylenes (73). From a pharmacological point of view Anise oil shows bronchodilator (74), anti-inflammatory (75) and antimicrobial (76) activities. New research shows the essential oil, aqueous, and ethanol extracts of Anise to have bronchodilator activities

while showing the inhibitory effects on muscarinic receptors as the underlying mechanism (77). Also, in a recent study, Domiciano et al. have suggested that anethole extracted from Anise can control non-immune acute inflammation through its inhibitory effect on production or release of prostaglandin E_2 (PGE_2) and NO. So Anise with bronchodilator and anti-inflammatory properties can be effective in the treatment of asthma (78). A study by Iannarelli et al. showed that the essential oil of Anise could significantly decrease pro-inflammatory cytokines (IL-1 and IL-8) in primary airway tracheal and bronchial epithelial cell lines (7).

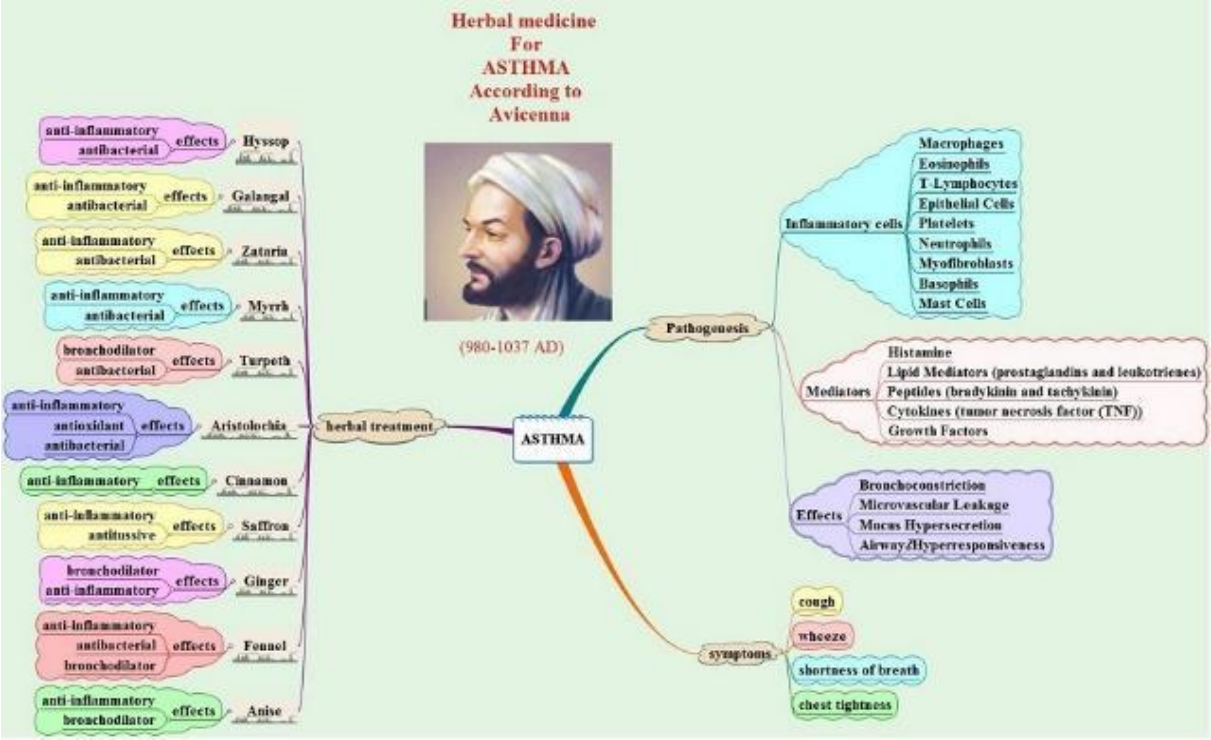

Fig. 1: Herbal medicine for ASTHMA according to avicenna

4- CONCLUSION

Asthma is a disease with a high prevalence that runs a chronic course. Ongoing efforts to find a safe way for managing asthma without any side effects were not successful. On the contrary, plants for the management of asthma presented in this study are supported by classical Iranian traditional texts as well as recent investigations. According to the mentioned studies the Hyssop, Saffron, Ginger, Anise and Fennel have the highest pharmacological effects and role in the treatment of asthma. The herbal drugs prepare a proper complementary and alternative to conventional medications, with fewer complications. Various activities such as; anti-inflammatory, bronchodilator, antitussive and etc. have been proposed by scientific studies on traditionally applied antiasthma plants. Future clinical studies on healthy volunteers and also patients suffering from asthma and reactive airway disease are compulsory to confirm the effectuality of these plants as complementary interventions in asthma. It seems that some of the components of these plants can be employed for designing new drugs.

Table-1: Medicinal plants used in Iranian traditional medicine for asthma.

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
Hyssopus officinalis L.	Lamiaceae	Hyssop	*Zoopha*	Evaluation of Antioxidant Activities and Phenolic Profile	77.72 ± 1.83	In vitro/ The antioxidant activity evaluated using the DPPH bleaching method, TEAC assay, EPR spectroscopy method	Positive (*Ocimum basilicum* and *Teucrium chamaedrys)*	30 min of incubation at 40 °C in a thermostatic bath	Ethanolic extract	Antioxidant activity values by TEAC method *T. chamaedrys> H. officinalis> O. basilicum*	Antioxidant (Vlase et al., 2014)
				Serum IL-17 level and balance of Th1/Th2 of asthma	0.04 g/10 g body weight	In vitro/ rats/ level of serum IL-17,IL-4 and IFN-γ were detected with ELISA	Positive (normal, asthma stimulated by (OVA) and dexamethasone group)	Once per day for eight weeks	Water extract	Inhibit the secretion of IL-17 and correct the imbalance between Th1/Th2 cytokines	Anti-inflammatory (Hou et al., 2010)
				T-bet, GATA-3, STAT-3 mRNA	0.04 g/10 g body weight	In vitro/ rats/ level of T-bet, GATA-3, STAT-3 mRNA were detected with RT-PCR	Positive (normal, asthma stimulated by (OVA) and dexamethasone group)	Once per day for eight weeks	Water extract	Expression of T-bet, GATA-3, STAT-3 mRNA of model group rats significantly reduced	Anti-inflammatory (Wang et al., 2011)
				Inhibiting airway inflammation and immune regulation	0.04 g/10 g body weight	In vitro/ BALB/c mice /	Positive (normal, chronic asthmatic, dexamethasone groups)	Once per day for eight weeks	Water extract	Inhibiting the invasion of EOS and decreasing the levels of IgE	Airway immune regulator (Ma et al., 2014b)
				Serum Eotaxin-2, Eotaxin-3 and sP-selectin levels	0.04 g/10 g & 1.6 g/10 g body weight,	In vitro/ rats/ The levels of serum Eotaxin-2, Eotaxin-3 and sP-selectin were determined with ELISA	Positive (normal, asthma stimulated by (OVA) and dexamethasone group)	Once per day for eight weeks	Water extract	Inhibit the secretion of Eotaxin-2, Eotaxin-3 and sP-selectin	Anti-inflammatory (Min, H. et al., 2009)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
				Airway remodeling	0.04 g/10 g	In vitro/ BALB/c mice/ detection of the expressions of MMP-9 and TIMP-1 and the morphological changes	Positive (control, airway remodeling, dexamethasone, and *Hyssopus officinalis* L. groups)	Once per day for eight weeks	Water extract	Inhibit airway remodeling by correcting imbalance of MMP-9/TIMP-1 ratio	Regulate MMP-9/TIMP-1 ratio (Ma et al., 2014a)
Alpinia galangal L.	Zingiberacea	Galangal	*Khulenjan*	Acetoxy chavicol acetate (ACA) and asthma	50 mg/kg/day ACA	In vitro/ BALB/c mice/ detected with ELISA	Positive (control, dexamethasone, and *Alpinia galangal* groups)	Once per day for 5 days	ACA isolated from the methanol extracts	Inhibited expression of the Th2 cytokines interleukin (IL)-4 and IL-13, and Th1 cytokines IL-12α and INF-γ	Anti-inflammatory (Seo et al., 2013)
				Hydroxychavicol acetate (HCA) and ACA in cytokine production	Various concentrations of either HCA or ACA In Th cell	In vitro/ Single cell suspensions were isolated from lymph nodes and spleens of wild type and T-bet KO mice, /detected with RT-PCR and ELISA	Negative	For 24, 48, or 4 days	HCA, ACA isolated from the methanol extracts	ACA increased cell apoptosis and antioxidant activity HCA suppressed T-bet expression, IL-2 And IFNγ	Anti-inflammatory Antioxidant (Min, H.J. et al., 2009)
Zataria multiflora Boiss.	Lamiaceae	Zataria	*Avishan-e-Shirazi*	Lung inflammation changes and oxidative stress	*Z.* dose 1 = 0.4 mg/mL, *Z.* dose 2 = 0.8 mg/mL, *Z. dose 3 = 1.6 mg/mL*, carvacrol dose1= 60 µg/mL, carvacrol dose2= 120	In vitro/ guinea pigs/ IL-8 was measured by ELISA and WBC was counted in duplicate in a hemocytometer	Positive/ 9 groups (Control, COPD, COPD + dexamethasone, COPD + *Z. multiflora* dose 1, COPD + *Z. multiflora* dose 2, COPD + *Z. multiflora* dose 3, COPD + carvacrol dose 1, COPD + carvacrol dose 2,	The extract, carvacrol, or dexamethasone, were added to the drinking water daily for 3 months	Hydro-ethanolic extract	preventive effect of *Z. multiflora* and carvacrol on differential WBC, levels of IL-8 of animal model of COPD, preventive therapeutic potential for *Z. multiflora* and its constituent,	Anti-inflammatory and anti-COPD (Boskabady and Mahtaj, 2015)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
					µg/mL, carvacrol dose3= 240 µg/mL		COPD + carvacrol dose 3)			carvacrol on lung inflammation and oxidative stress in COPD	
				Zataria multiflora affect tracheal responsiveness, serum levels of NO, nitrite, PLA2, TP and histamine	Extract 1= 0.2 mg/ml, Extract 2= 0.4 mg/ml, Extract 3= 0.8 mg/ml	In vitro/ guinea pigs/ Serum histamine, and PLA2 levels were measured by ELISA, serum protein level by quantitative2 protein assay kit	Positive/ 5 groups (Control, Sensitized, S + Extract 1, S + Dexamethasone, (50 µg/ml) S + Extract 2, S + Extract 3).	daily for 35 days	Ethanolic extract	preventive effect on tracheal responsiveness, serum level of NO, nitrite, total protein, PLA2 and histamine	Anti-inflammatory (Boskabady, Mohammad Hossein et al., 2014)
				Th_1/Th_2 cytokine (IFN-γ/IL4) balance	0.2 mg/mL	In vitro and in vivo/ Cells were counted with a Hemocytometer, RNA extraction and real-time RT-PCR analysis, IL-4 and IFNγ by ELISA	Positive/ 6 groups	daily for 14 days	Ethanolic extract	Increase in IFNγ and a decrease in IL-4, gene expression and enhanced the ratio of IFNγ to IL-4 (Th1/Th2 balance)	Anti-inflammatory (Boskabady et al., 2013)
Commiphora myrrha (Nees) Engl.	Burseraceae	Myrrh	*Murr*	Inhibition of LPS-Induced Inflammatory Response	0.1 mg/mL	In vitro/ Murine peritoneal macrophages were stimulated with 100 ng/mL of LPS/ TNF-α, IL-1β, and IL-6 by ELISA and RT-PCR, PGE_2 by immunoassay kits	Negative	24 h	Water extract	Inhibition of NO, PGE_2, and TNF-α production through inhibition of JNK pathway. Inhibition of productions of NO, PGE_2, TNF-α, IL-1β, and IL-6	Anti-inflammatory antibacterial (Kim et al., 2011)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
Ipomoea turpethum R. Brown	Convolvulaceae	Turpeth	*Torbod*	Evaluation of the antioxidant potential	1 mg/ml	In vitro/ The antioxidant activity was evaluated by the phospho-molybdenum method by using a spectrophotometer	Negative	90 min	Ethanolic extract	Radical scavenging and antioxidant activities, as determined by scavenging effect on the OH radical, reducing power, FRAP& Superoxide assay.	Antioxidant (Sharma and Singh, 2012)
				Evaluation of antidiarrhoeal, antispasmodic and bronchodilator activities	1 g/kg	In vitro/ Castor oil-induced diarrhoeal mice model and isolated tissue: rabbit jejunum and guinea-pig tracheal.	Positive (control and 4 groups that received different dose)	24 h for mice, 30 min for rabbit jejunum, 45 min for guinea-pig tracheal.	Ethanolic extract	antispasmodic and bronchodilator properties that mediated possibly through the presence of Ca^{++} antagonist	Antispasmodic Bronchodilator (Shareef et al., 2014)
Aristolochia clematitis L.	Aristolochiaceae	Aristolochia/ Birthwort	*Zaravand*	Free radical scavenging activity and kinetic behavior	0.078 mg/mL	In vitro/ Determination of free radical scavenging activity by HPTLC and DPPH methods	Positive (Diethyl ether extract, Methanolic extract in 4 concentrations, Water extract)	0.078 (mg/mL): 112 min/ 0.156: 89 min/ 0.312: 60 min/ 0.625: 13 min	Methanolic extract	Tannin extract displayed strong antioxidant activity as ascorbic acid and methanolic extract.	Antioxidant (Benmehdi et al., 2013)
				Anti-inflammatory activity from constituents of *Aristolochia clematitis* L.	10 µg/mL	In vitro/ Analysis by HPLC method. A reversed-phase HPLC method	Positive (Control cells stimulated with LPS)	-	petroleum ether (PE) extract, dichloromethane (DCM) extract,	Inhibition of the IL-6 and TNFa	Anti-inflammatory (Desai et al., 2014)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
									ethyl acetate (EA) extract, methanol (MeOH) extract		
Cinnamomum verum J.Presl.	Lauraceae	Cinnamon	*Darchini*	Anti-inflammatory activity of cinnamon	20 mg/kg body weight	In vivo and in vitro LPS-induced models/ BALB/c mice/ TNF-α and IL-6 by ELISA and RT-PCR,	Positive	6 days	water extract	Decreasing the serum levels of TNF-α and IL-6. CWE treatment *in vitro* decreased the mRNA expression of TNF-α.	Anti-inflammatory (Hong et al., 2012)
Crocus sativus L.	Iridaceae	Saffron	*Zaffaran*	Evaluation of the antitussive effect of saffron and its components	Saffron: 100 mg/kg/ safranal: 0.25 ml/kg	In vivo /guinea pigs	Positive	10 min	Ethanolic extract	Reduction the number of coughs	Antitussive (Hosseinzadeh and Ghenaati, 2006)
				The effect of the extract of saffron and its components safranal, on lung pathology and lung inflammation	Saffron: 0.1 mg/ml, safranal:4 µg/ml	In vivo and in vitro /guinea pigs/ Serum histamine levels were determined by Histamine ELISA kit	Positive (control, dexamethasone group & 6 groups with different concentrations)	18 ± 1 days	Hydro-ethanolic extract	Prophylactic effect for the extract of the plant and safranal on asthma	Anti-inflammatory (Boskabady et al., 2012)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
				Preventive effects of saffron on hematological parameters on asthma	50 mg/kg, 2 times a week	In vivo and in vitro / rats	Positive (Control, not sensitized, asthma, asthma+50EX, asthma+100EX, asthma+200EX)	32 days	Hydroalcoholic extract	The extract reduced WBC count and eosinophil percentage	Anti-inflammatory (Vosooghi et al., 2013)
				Safranal and inducible Nitric Oxide synthase and Asthma	1 mg/kg, once a day	In vitro/ Normal human bronchial epithelial cells (NHBE)/ In vivo/ Balb/c mice/ Measurements of IL-5 and IL-13 by ELISA	Positive	A week	Methanol water extract	Decreasing in airway hyper-responsiveness and airway cellular infiltration to the lungs, reducing iNOS production, bronchial epithelial cell apoptosis, and Th2 type cytokine production	Antioxidant Anti-inflammatory (Bukhari et al., 2015)
				Relaxant effect of saffron on trachea	0.15 mg/ml	In vitro/ guinea-pig (tracheal chains)/ responses were recorded on a kymograph	Positive (control and 2 groups, theophylline and safranal)	7 minutes after the contraction of the trachea	Ethanolic extract	The relaxant effect of this plant could be due to b-adrenoceptor stimulatory, muscarinic and/or histamine (H1) receptor inhibitory effect	Bronchodilator (Boskabady and Aslani, 2006)
				Saffron on tracheal responsiveness and plasma levels of IL-4, IFN-γ, total NO and nitrite	20 mg/kg/day	In vivo and in vitro / guinea-pig/ IL-4, IFN-γ were measured by ELISA and NO level was determined by Nitric Oxide Calorimetric	Positive (control, extract of Saffron + dexamethasone, extract alone)	exposion to an aerosol of 4% OVA for 18±1 day	Hydro-ethanolic extract	Preventive effect of Saffron extract on tracheal responses and serum levels of inflammatory mediators and increased Th_1/Th_2	Anti - inflammatory Anti-oxidant (Byrami et al., 2013)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
						Assay kit				balance	
				Effect of safranal on tracheal responsiveness, serum levels of cytokines, total NO and nitrite	16 mg/mL	In vivo and in vitro / guinea-pig/ IL-4, IFN-γ were measured by ELISA and NO level was determined by Nitric Oxide Calorimetric Assay kit	Positive (control, dexamethasone, 3 concentrations of safranal)	exposion to an aerosol of 4% OVA for 18±1 day	Safranal, a constituent of saffron	Preventive effect for safranal on tracheal responses and serum cytokine, total NO and nitrite levels and increase Th1/Th2 balance	Anti - inflammatory (Boskabady, M. H. et al., 2014)
Zingiber officinale Roscoe	Zingiberacea	Ginger	*Zangabil*	Ginger and Its constituents on airway smooth muscle relaxation	Ginger: 50 mg/ml, Gingerol and shogaol: 100 µM	In vitro/ Human Airway Smooth Muscle Cells and Guinea Pig Tracheal Rings	Positive (control, ginger and constituents)	15 min	Food-grade ginger, gingerol, and shogaol constituents of ginger	ginger and its isolated active components relax ASM and attenuates airway hyperresponsiveness, by altering $[Ca^{2+}]$ regulation	Bronchodilator (Townsend et al., 2013)
				Ginger and airway remodeling	Gingerol and shogaol: 5µM	In vitro/ Two human bronchial epithelial cell lines, BEAS-2B and HBE135-E6E7	Positive	1 h	Gingerol, and shogaol constituents of ginger	Gingerol, and shogaol suppress phthalate ester-mediated airway remodeling	Anti - inflammatory (Kuo et al., 2011)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
				Ginger and Th2-mediated immune responses	500 mg/kg	In vivo and in vitro /BALB/c mice /evaluation of mRNA expression levels and Th2 type markers by RT-PCR and ELISA	Positive (control, ginger and methylprednisolone)	7 days	Ethanol extract	Ginger suppressed Th2-mediated immune responses and could play a role in the management of allergic asthma	Anti - inflammatory (Ahui et al., 2008; Khan et al., 2014)
Foeniculum vulgare Mill.	Apiaceae	Fennel	*Razianeh/ Badian*	Antioxidant protection and fennel	Plant (5 g) and 150 mL of water	In vitro/ DPPH assay test	Positive	1 min, 3 min and 5 min	Dried commercial fennel and beverages	Foeniculum vulgare is an effective antioxidant	Antioxidant (Kontogiorgis et al., 2016)
				Foeniculum vulgare and Lipopolysaccharide stimulated Macrophage	100 µg/m	In vitro/ RAW 264.7 mouse macrophage/ Cytotoxicity was assessed using a colorimetric assay, IL-1β, IL-6, and TNF-α by ELISA-	Positive	1 h	Methanol extract	F. vulgare inhibitions of the productions of NO, PGE2, and pro-inflammatory cytokine	Anti - inflammatory (Yang et al., 2014) (Lee, 2004)
				Possible mechanism(s) for relaxant effects of *Foeniculum vulgare*	0.1 ml	In vitro/ tracheal muscles of guinea pigs	Positive	10 min	Ethanol extract	Potassium channel opening effect for this plant, which may contribute on its relaxant effect	Broncho dilatory (Lee, 2004)
Pimpinella anisum L.	Apiaceae	Anise	*Anisoon*	Antispasmodic and relaxant effects of the hydroalcoholic extract of *Pimpinella anisum*	5 µg/mL	In vitro/ Male Wistar rats/ analysed: the E_{max} (maximal effect generated by the	Positive	30–45 min	Hydroalcoholic extract	*Pimpinella anisum* involve the participation of NO and subsequent activation of the NO-cGMP	Bronchodilator (Tirapelli et al., 2007)

Medicinal plant	family	Common name	Traditional name	Subject	minimal active concentration	model used	control	Duration	type of extract	Results	Pharmacological effects
						agonist) and Pd_2 (−log EC50)				pathway	
				Anti-inflammatory effects of anethole in lipopolysaccharide-induced acute lung injury	62.5 mg/kg	In vitro/ BALB/C mice/ measuring total protein and cell levels and inflammatory mediator production by histological evaluation and Western blot analysis	Negative control	4 h	Anethole a major component of the essential oil of star anise	Decreasion of the total protein concentrations; numbers of neutrophils and macrophages; MMP-9, TNF-α and NO and LPS-induced histopathological changes.	Anti-inflammatory (Kang et al., 2013)
				Possible Mechanism for the Relaxant Effect of *Pimpinella anisum*.	0.1 ml	In vitro/ tracheal chains of guinea pig	Negative control and positive control	10 min	Ethanol extract	Inhibitory effects on muscarinic receptors	Bronchodilator (Boskabady and Ramazani-Assari, 2005)
				Inhibitory effect of anethole in nonimmune acute inflammation	250 mg/kg	In vitro/ Male Wistar rats and male Swiss mice/ measuring IL-1β, IL-6, and TNF-α by ELISA	positive	6 h	Anethole a major component of the essential oil of star anise	Inhibitory effect on production or release of prostaglandin E_2 (PGE_2) and NO	Anti-inflammatory (Domiciano et al., 2013)

5- Acknowledgements: None

6- Declaration of interest

The authors declare that there are no conflicts of interest.

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