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Review Article

A Review of Medicinal Plants with Broncho-Dilatory Effect-Part 1

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Abstract: Medicinal plants with bronco-dilatory effects are beneficial for patients with asthma, chronic obstructive air way disease, pulmonary emphysema and many other complains. Previous reviews revealed that there are many medicinal plants possessed respiratory smooth muscle relaxant effects. This review was designed to highlight the bronco-dilatory effects of medicinal plants.
Keywords: medicinal plants, bronco-dilatation pharmacology, relaxation, smooth muscles.

INTRODUCTION

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavors, fragrances, colors, bio-pesticides and food additives. A lot of plant active ingredients were isolated and characterized, and their pharmacological effects and mechanisms of action were understood [1-25].

Medicinal plants with bronco-dilatory effects are beneficial for patients with asthma, chronic obstructive air way disease, pulmonary emphysema and many other complains. Previous reviews revealed that there are many medicinal plants possessed respiratory smooth muscle relaxant effects. This review was designed to highlight the bronco-dilatory effects of medicinal plants [26-30].

PLANTS PROFILE

Ailanthus altissima

The effect of *Ailanthus altissima* swingle (ailanthic cortex, AAS) on the mast-cell-mediated allergic and inflammatory reaction was studied using *in vivo* and *in vitro* models and elucidate its molecular mechanisms. AAS significantly inhibited compound 48/48-induced edema and systemic anaphylaxis. AAS significantly inhibited passive cutaneous anaphylaxis. AAS inhibited histamine release from rat peritoneal mast cells (RPMCs) in a dose-dependent manner. Moreover, AAS significantly inhibited production of inflammatory cytokines, tumor necrosis factor (TNF), interleukin (IL)-6, and IL-8 on the phorbol 12-myristate 13- acetate and calcium ionophore A23187 (PMACI)-stimulated human mast cell line, HMC-1 cells. AAS inhibited the IgE or stem cell factor-induced TNF production on RPMCs. In activated HMC-1 cells, the expression level of NF-kappaB/Rel A protein increased in the nucleus, whereas the level of NF-kappaB/Rel A in the nucleus was decreased by AAS treatment. In addition, AAS inhibited the PMACI-induced IkappaBalpha degradation [31-32].

Allium cepa

Ether and ethanolic extract of the fresh bulb inhibited allergen and platelet activating factor-induced asthmatic reactions when administered intragastrically to guinea pigs [33-34]. Oral administration of an ethanol extract to guinea-pigs inhibited tracheal smooth muscle contractions induced by carbachol, and inhibited histamine-, barium chloride-, serotonin-, and acetylcholine-induced contractions in the ileum [35]. Five alk(en)ylsulfinothioic acid alk(en)yl-esters isolated from onions and four synthetic thiosulfinates inhibited 5-lipoxygenase of porcine leucocytes, histamine release and leukotriene B4 and C4 biosynthesis of human polymorphonuclear leucocytes, thromboxane B2 biosynthesis by human platelets and allergen- and PAF-induced bronchial obstruction of guinea-pigs. According to the results the authors postulated that the anti-asthmatic and anti-inflammatory effects of onions depend in part on the thiosulfinate moiety [36]. On the other hand, the effect of onion extracts on bronchial obstruction (BO) induced by inhalation of ovalbumin in guinea-pigs was investigated. Bronchial obstruction was measured by whole body plethysmography. Benzyl-isothiocyanate (BITC) inhibited BO in a dose-dependent fashion: 150 mg/kg: 89%; 75 mg/kg: 76%; 30 mg/kg: 66%; 15 mg/kg: 49%. Ethyl-isothiocyanate and allyl-isothiocyanate showed similar effects, while, p-hydoxy-benzyl-isothiocyanate, was ineffective.

Additional experiments showed no antagonistic effects for the crude onion extract on histamine- or acetylcholine-induced BO. The authors mentioned that the antiasthmatic effects of onions mediated at least in part by isothiocyanates [37].

Althaea officinalis

The bronchodilatory effect of methanolic and aqueous extracts of the root Althaea was assayed at different concentrations (0.2, 0.6, 2.6, 6.6, 14.6 µg/ml) and epinephrine (5 µm) in the presence and absence of propranolol (1 µM) under one g tension based on the isometric method. The assay was recorded in an organ bath containing Krebs-Henseleit solution for tracheobronchial smooth muscle contractions using potassium chloride (KCl) (60 mM) induction. Epinephrine (5 µm) alone and root methanolic and aqueous extract concentrations (0.6-14.6 µg/ml) reduced tracheobronchial smooth muscle contractions induced using KCl (60 mM) in a dose dependent manner. Propranolol inhibited the antispasmodic effect of epinephrine on tracheobronchial smooth muscle contractions, but could not reduce the antispasmodic effect of the root extract concentrations. The authors concluded that the methanolic and aqueous extracts of Althaea root inhibited the tracheobronchial smooth muscle contractions of rats in a dose dependent manner, but B-adrenergic receptors do not appear to engage in this process [38-39].

Ammi visnaga

Khella's antispasmodic properties are also useful to treat asthma attacks. During the 1950′s, research into khella's usefulness as an asthma treatment led to the creation of many asthma medications containing khellin and visnagin [40-42].

Andrachne aspera

Root extracts of *Andrachne aspera* showed significant spasmolytic activity on tracheal muscle of cat, and antihistaminic activity [43-44].

Anthemis nobelis

In an open clinical study carried out on 54 patients with chronic bronchial asthma, *A. nobilis* showed antiasthmatic effects, it caused significant elevation in the values of forced expiratory volume in first second (FEV1%) and forced volume capacity (FVC) with marked reduction in asthmatic attacks [45-46] .

Bacopa monnieri

Bacopa *monnieri* has relaxant effects on pulmonary arteries, aorta, trachea and bronchial smooth muscles in experimental animals. These effects possibly mediated by inhibition of calcium-ion influx into cell membranes [47-49]. The methanol extract of Bacopa possessed potent mast cell stabilizing activity comparable to disodium cromoglycate [50-51].

Benincasa hispida

Two triterpenes, namely alonusenol and multiflorenol extracted from the methanolic extract of *B. hispida* fruit exhibited mast cell stabilizing effect and found to have potential inhibitory effect on the histamine release induced by antigen antibody reaction [52].

Methanol extract of *Benincasa hispida* (MEBH) showed excellent protection in guinea pigs against the histamine-induced bronchospasm even at a very low dose, 50 mg/kg orally. However, even at a higher dose level 400 mg/kg, MEBH did not significant protect against acetylcholine- induced bronchospasm. The results suggest that the protective effect against bronchospsam induced by histamine aerosol may be mediated by antihistaminic activity (H**1** receptor antagonism) [53-54].

Bryophyllum calycinum

The methanol extract of the *leaves* has also been reported to have histamine receptor (H1) antagonism in the ileum, peripheral vasculature and bronchial muscle [55-56]**.**

Capparis spinosa

The bronchorelaxant effects of *Capparis spinosa* was studied on the rings of windpipes of rat. The addition of *Capparis spinosa* extracts (0.1, 1 and 10 mg/ml) during the step of contraction by acetylcholine showed various effects on trachea. Incubation of the windpipe for 30 min with extracts proves to be so efficient. The dose of 10 mg/ml from fruits and seeds extracts showed a significant relaxant effect. The results showed a potent relaxant effect of the fruit aqueous extract of *Capparis spinosa*, on rat trachea, with a dose dependant manner. However, the leaf aqueous extract has a contractive effect. A muscarinic receptor blockade / stimulation was suggested for *Capparis spinosa* leaf extracts [57-58].

Capsicum frutescens* and *Capsicum frutescens

Capsaicin produces a protective effect in rat lung by strengthening the pulmonary antioxidant enzyme defense system. Capsaicin treatment caused desensitization of the respiratory tract mucosa to a variety of lung irritants [59-60].

Carum carvi

The bronchodilatory effects of the aqueous extract (AE), macerated extract (ME), essential oil (EO) of caraway, and 4/µM theophylline (T) in comparison with saline (S) were examined by their relaxant effects on precontracted [by 10 /µM methacholine (M)] of the isolated tracheal chains of guinea pigs. The bronchodilatory effect of AE, ME, and EO was lower than that of T ($p<0.00l$ for all cases), but it was significantly higher than the effect of S ($p<0.05$ for AE, $p<0.01$ for ME, and $p<0.005$ for EO). The results indicated that the bronchodilatory effect was mainly

due to the non-competitive antagonistic property of this plant at muscarinic receptors. The β- stimulatory effect and/or anti-histaminic effect of EO might be contributed to its non-competitive property [61-62].

Citrus fruits

A study among British children found a positive association between fresh fruit consumption and the level of forced expiratory volume in one second (FEV1). The association was more pronounced in wheezers than non-wheezers [63].

An Italian study, followed over 18,000 children aged 6-7 years and found that those eating the most citrus fruit (oranges, tangerines, and grapefruit), along with kiwifruit, had a reduced risk of wheezing. The protective effect of citrus did not appear to be dose related. The authors attributed the lung health benefiting properties of citrus and kiwifruit to their high concentration of vitamin C[64].

Cordia myxa

The mechanism of broncho-relaxant effect of *Cordia myxa* was studied in sheep trachea. *Cordia myxa* extract inhibited contraction in both epithelium-intact and denuded sheep trachea rings induced by acetylcholine. The scale of relaxation with *Cordia myxa* extract was dose dependent and slightly more potent in epithelium denuded rings than epithelium-intact preparations. L-NAME (10 nM-100 uM) but not DNAME completely inhibited the relaxant effect in a concentration dependent manner. *Cordia myxa* extract -induced relaxation was inhibited by methylene blue (1 - 100 uM), and verapamil (100 nM), and removal of extracellular Ca^{2+}. In contrast, *Cordia myxa* extract -induced relaxation was potentiated by Nw-nitro-Larginine (L-NOARG) treatment. Accordingly, the *Cordia myxa* extract -induced relaxation may be due to nitric oxide from aupplied exogenously administered L-arginine as well as endogenous nitric oxide donors such as amino acid and arginine derivatives [65-66].

Cressa cretica

The effect of ethylacetate fraction (Fr-Et) and methanolic fraction (Fr-Me) obtained from *Cressa cretica* were evaluated in experimental models for bronchodilatory activity and mast cell stabilising activity. The effect of Fr-Et and Fr-Me were studied on acetylcholine and histamine aerosol-induced broncospasm using guinea pigs as an experimental animals. Also, the effects of these fractions were evaluated on the isolated guinea pig tracheal preparations. Besides this, mast cell degranulation effect was assessed using egg albumin and compound 48/80 on rat peritoneal mast cells. Significant increase in preconvulsion time was observed due to pretreatment with the fractions when guinea pigs were exposed to histamine and acetylcholine aerosol. Fr-Et and Fr-Me significantly increased the preconvulsion in a dose depended manner that suggestive of bronchodilating activity. Fr-Et and Fr-Me exhibited a significant concentration dependant relaxant effect on guinea pig trachea pre-contracted with CCh, K^+ and histamine. The results revealed that Fr-Et was more potent than Fr-Me in relaxing histamine, K^+ and calcium induced contraction than CCh induced contractions. In styding the effect of the fractions in protecting mast cell degranulation, which were elicited by the egg albumin as well as synthetic compound 48/80 revealed that both fractions significantly protect the mast cell degranulation, which release mediators such as histamine and proinflammatory cytokines through various stimuli, in a dose depended manner [67-68].

Crocus sativus

The prophylactic effect of the extract of *Crocus sativus* and its constituent, safranal on the respiratory system of sensitized guinea pigs was examined. Guinea pigs were sensitized with injection and inhalation of ovalbumin (OA). One group of sensitized guinea pigs were given drinking water alone (group S) and three groups were given drinking water containing three concentrations of safranal (S+SA1, S+SA2 and S+SA3 groups), three groups, drinking water containing three concentrations of extract (S+CS1, S+CS2 and S+CS3 groups) and one group drinking water containing one concentration of dexamethasone (S+D group). Treatment of S animals with dexamethasone, all concentrations of the extract and safranal significantly improved lung pathological changes, WBC and serum histamine levels compared to group S ($p<0.05$-0.001). Treatment of S group with first concentration of safranal also decreased total WBC. Treatment with safranal was more effective in improvement of most pathological changes, total and differential WBC count as well as serum histamine level ($p<0.05$-0.001). These results indicated a preventive effect of the extract of *Crocus sativus* and its constituent safranal on lung inflammation of sensitized guinea pigs [69-70].

The effect of the extract of *Crocus sativus* and one of its constituents, safranal, on the inflammatory changes of sensitized guinea pigs was examined. Eight groups of sensitized guinea pigs to ovalbumin were studied. One group was given drinking water alone (group S), while other 7 groups were received drinking water containing; three concentrations of safranal (4, 8 and 16 μg/ml), three concentrations of extract (0.1, 0.2 and 0.4 mg/ml) and one concentration of dexamethasone (S+D group). Total and differential white blood cell (WBC) counts in blood were evaluated. Total blood WBC number, eosinophyl and lymphocyte percentage in blood were increased, but neutrophil decreased in sensitized animals compared to those of control groups ($P<0.05$ to $P<0.001$). Treatment of animals with dexamethasone, all concentrations of the extract and safranal significantly improved most types of WBCs but total WBC number was only decreased in treated groups with dexamethasone and

high concentration of the extract compared to group S (P<0.05 to P<0.001). Safranal was more effective in the improvement of eosinophil and lymphocyte compared to the extracts (P<0.001 for both cases). However, the preventive effect of the extract of *Crocus sativus* on total WBC count was more prominent than that of the safranal (p<0.01) [71].

The effect of the extract of *Crocus sativus* and its constituent, safranal on inflammatory markers in sensitized guinea pigs was examined. Ovalbumin (OA) sensitized guinea pigs were given drinking water alone (group S), or drinking water containing three concentrations of safranal, three concentrations of extract and one concentration of dexamethasone, (n=6, for all groups) and serum levels of endotheline-1 (ET-1) and total protein (TP) were assessed. Serum levels of group S were significantly higher than control group (P<0.01 for ET-1 and P<0.001 TP). Treatment of group S animals with dexamethasone, most concentrations of the extract and safranal significantly reduced serum levels of ET-1 and TP compared to group S (P <0.01 to P <0.001). The effects of one concentration of the extract and safranal were significantly higher than dexamethasone (P <0.05 to P <0.01) [72].

The prophylactic effect of saffron (*Crocus sativus*) in asthma was examined in ovalbumin sensitized rats. The sensitized rats were pretreated with three different concentrations of extract, 50, 100, and 200 mg/kg. Total WBC number, eosinophil and neutrophil percentage in blood were increased, but lymphocyte decreased in sensitized animals compared with those of control group (p<0.05 to p<0.001). In addition to elevation of RBC and platelet counts after sensitization in the asthma group. Pretreatment of sensitized rats in all concentrations decreased WBC count which was significant in first two concentrations (p<0.01 compared with asthma group). All concentrations of extract decreased eosinophil percentage significantly (p<0.001 compared with asthma group), however, for neutrophil percentage this improvement was not significant. Lymphocyte percentage increased in group asthma +100EX compared with asthma group (p<0.05). Moreover, in all concentrations, the extract reduced RBC and platelet count in pretreated sensitized rats compared with group of asthma (p<0.01 to p<0.001) [73].

The effects of *Crocus sativus* extract on total and differential white blood cells (WBC) count in lung lavage fluid (LLF) was studied in ovalbumin-sensitized rats. Total WBC count, neutrophil, and eosinophil percentage in LLF were increased in sensitized animals compared with the control group (p<0.001). Treatment of sensitized animals with all doses of the extract significantly reduced WBC number and the percentage of neutrophil and eosinophil compared with the sensitized animals (p<0.01-0.001). According to the results, the extract of *Crocus sativus* could be effective on alleviating lung inflammatory cells specially eosinophils in lung lavage of sensitized animals which may indicate a preventive effect against lung inflammation in asthma [74].

The preventive effects of the extract of *Crocus sativus* on tracheal responsiveness and plasma levels of IL-4, IFN-γ, total NO and nitrite were examined on sensitized guinea pigs. Methacholine and ovalbumin (OVA) sensitized guinea pigs, were given drinking water containing three concentrations of the extract of *Crocus sativus*. The TR to both methacholine and OVA significantely increased the levels of serum IL-4, total NO and nitrite, but that of IFN-γ and IFN-γ/IL-4 ratio (Th1/Th2 balance) were decreased compared to the controls (p<0.05 to p<0.001). In the treated animals with dexamethasone and all concentrations of the extract, TR to both methacholine and OVA, IL-4, total NO and nitrite were significantly decreased but IFN-γ and IFN -γ/IL-4 ratio increased (p<0.05 to p<0.001). The effects of the highest concentration of the extract was greater than those of other concentrations and dexamethasone (p<0.05 to p<0.01) [75].

The relaxant effects of aqueous-ethanolic extracts of *Crocus sativus* and one of its main constituents, safranal, were examined on guinea-pig tracheal chains. The relaxant effects of four cumulative concentrations of aqueous-ethanolic extract (0.15, 0.3, 0.45, and 0.60 g %) and safranal (0.15, 0.30, 0.45, and 0.60 ml 0.2 mg/ml solution) in comparison with saline, as negative control, and four cumulative concentrations of theophylline (0.15, 0.30, 0.45, and 0.60 mM), as positive control, were examined using guinea-pig precontracted tracheal chains. The tracheal chains had been precontracted by three different methods. Group 1 had been precontracted using 10 microM methacholine. The other two groups had been precontracted using 60 mM KCl at two different conditions: non-incubated tissues (group 2) and tissues incubated with 1 microM propranolol, 1 microM chlorpheniramine and 1 microM atropine (group 3). In group 1 all concentrations of theophylline, extract and safranal showed significant relaxant effects compared with saline (p<0.05 to p<0.001). In group 2 theophylline, extract and safranal showed concentration-dependent relaxant effects also compared with saline (p<0.05 to p<0.001 for different concentrations except two low concentrations of safranal). However, in group 3 the extracts of *Crocus sativus* showed a weak relaxant effect (p<0.05 only for the highest concentration). The effects of the last concentration of safranal (0.60 ml 0.2 mg/ ml solution) in group 1, and all its concentrations in group 2 were significantly lower than those of theophylline (p<0.05 to p<0.001). In addition, the effects of safranal 0.45 and 0.60 ml 0.2 mg/ ml solution in groups 1 and 2 were significantly lower than that of *Crocus sativus* extract. There were significant correlations between the relaxant

effects and concentrations for extract, safranal and theophylline in all experimental groups ($p<0.001$ for all cases). The authors concluded that *Crocus sativus* induced potent relaxant effect on tracheal chains of guinea-pigs that was comparable to or even higher than that of theophylline at the concentrations used. The results also indicated that safranal was, at least in part, responsible for the relaxant effect of *Crocus sativus* [76].

Cuminum cyminum

The relaxant effects of the macerated and aqueous extracts of *Cuminum cyminum* (0.25, 0.5, 0.75 and 1.0 g%) was investigated on the tracheal chains of guinea pig in comparison with saline and theophylline (0.25, 0.5, 0.75, and 1.0 mM) In Group 1 experiments (contracted by KCl) only the last two concentrations of theophylline and the highest concentration of macerated extract showed significant relaxant effect compared to that of saline ($p<0.001$ and $p<0.05$ for theophylline and macerated extract respectively). The effects of the last two concentrations of theophylline in this group were significantly greater than those of the macerated and aqueous extracts ($p<0.001$). However, in Group 2 experiments (contracted by methacholine) both the extracts and theophylline showed concentration-dependent relaxant effect compared to that of saline ($p<0.05$ to $p<0.001$). The effects of the two last concentrations of both extracts were significantly lower than those of theophylline in Group 2 experiments ($p<0.05$ to $p<0.001$). In Group 3 (non-incubated, contracted by methacholine) the extracts of *Cuminum cyminum* did not show any relaxant effect of tracheal chains. The relaxant effects of macerated and aqueous extracts in Groups 1 and 3 were significantly lower than those of Group 2 ($p<0.05$ to $p<0.001$)[77-78].

Cydonia oblonga

The crude extract of *Cydonia oblonga* seeds (Co.Cr) (0.01-10 mg/ml) relaxed CCh (1 μM) and K^+ (80 mM)-induced contractions of isolated rabbit tracheal preparations, similar to the effect produced by verapamil [79-80].

Cynodon dactylon

The bronchodilatory effect of *Cynodon dactylon* was investigated by *in vitro* and *in vivo* models. Acetylcholine (Ach)-induced bronchospasm was conducted in guinea pig while isolated rat tracheal strip was suspended in organ bath to measure the concentration response curve using multichannel data acquisition system. The chloroform extract of *Cynodon dactylon* (CECD) protected against Ach-induced bronchospasm in guinea pigs, similar to atropine. In the *in vitro* studies, CECD relaxed carbachol (CCh) and high K^+ -induced contraction of rat tracheal strip, similar to atropine and verapamil, suggesting antimuscarinic and calcium channel blocking (CCB) activities, which were confirmed by right ward shifting of CCh and Ca^{+2} concentration response curve (CRC). The phosphodiestrase (PDE) inhibitory activity was confirmed by potentiation of isoprenaline-induced inhibitory response, similar to papaverine. Densitometry analyses led to the identification of scopoletin as an active ingredient. It significantly inhibited high K^+, and Ca^{+2} induced contractile response, similar to verapamil. The phosphodiestrase inhibitory activity was confirmed by direct evidence of potentiation of isoprenaline-induced inhibitory response, similar to papaverine. The results revealed that the bronchodilator activity of CECD was partly due to presence of scopoletin, and mediated possibly through CCB and PDE inhibition [81-82].

CONCLUSION

This review was designed to cover the medicinal plants possessed respiratory smooth muscle relaxation to be utilize in the medical practice for the treatment of broncho-spasm as a result of effectiveness and safety.

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