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The effects of some medicinal plants on histamine (H_1) receptors

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Abstract: Medicinal plants have been identified and used as primary sources in prevention and treatment of diseases from ancient times due to its various pharmacological activities. In this review, the inhibitory effects of extracts, some fractions and some constituents of medicinal plants on histamine (H_1) receptors were reviewed. Various databases including; Medline, PubMed, Science Direct, Scopus, and Google Scholar were searched using inhibitory effect, histamine (H_1) receptor, medicinal plants and their constituent's keywords from 1974 to 2016. All studied plants including; *Nigella sativa*, *Rosa damascena*, *Thymus vulgaris*, *Carum copticom*, *Zataria multiflora*, *Crocus sativus*, *Portulaca oleraceae*, *Bunium persicum*, *Satureja hortensis*, *Ephedra sinica*, *Humulus lupulus*, *Combretum racemosum*, *Aegle marmelos*, *Ginkgo biloba* and *Eriobotrya japonica* showed a competitive antagonism effect on histamine (H_1) receptors. Therefore, the studied plants and their constituents could be of therapeutic values in clinical practice as antihistamines drugs.

Keywords: Inhibitory effect, Histamine (H_1) receptor, Medicinal plant

Introduction

Histamine is identified as one of the important mediators of inflammation and bronchoconstriction (Goyal RK 2003). In the living organism, histamine [4-(2-aminoethyl) imidazole] is synthesized from the naturally occurring-amino acid, histidine, by the loss of a carboxyl group through bacterial or enzymatic decarboxylation (Cooper et al., 2005). Histamine is released from degranulated mast cells. Targeting histamine, either prevention of its release from mast cells or use of histaminergic receptors antagonists becomes part of antihistaminic therapy (Satoskar et al., 1997). In human body histamine was presented in various biological fluids, in platelets, leucocytes, basophiles, and mast cells (Ellison, 2002). Major portion of histamine is stored in mast cells and circulatory basophiles (Rang et al., 2007). Release of histamine leads to contraction of smooth muscle, vasodilatation and increased vascular permeability (Kay, 2000; Kim et al., 2005). Histamine also acts as a neuromedulator participating in many cell physiological processes such as allergic reaction, inflammation, gastric acid secretion, central and peripheral neurotransmission (Barar, 2000).

Four human G-protein coupled histamine receptor subtypes ($H_{1–4}$) are currently known to mediate the various actions of this monoamine (Kay, 2000; Kim et al., 2005). Histamine when inhaled has been shown to induce bronchoconstriction by direct H_1-receptor activation and also by a naturally mediated bronchoconstrictor effect via vagal reflexes (Hajare et al., 2011). The histamine H_1 receptor has been an attractive target for drug discovery for several years and H_1 receptor antagonists have proved to be effective therapeutic agents for allergy and respiratory disorders (Saxena et al., 2006).

First-generation histamine H_1-receptor antagonists, such as diphenhydramine, triprolidine, hydroxyzine or chlorpheniramine, frequently cause somnolence or other CNS adverse effects. Second-generation H_1-antagonists, such as terfenadine, astemizole, loratadine and cetirizine, they have a more favourable benefit/risk ratio than their predecessors with regard to lack of CNS effects, and do not exacerbate the adverse CNS effects of alcohol or other CNS-active chemicals. The concept of a risk-free H_1-antagonist is proving to be an oversimplification. An H_1-antagonist absolutely free from adverse effects under all circumstances is not yet available for use. The magnitude of the beneficial effects of each H1-antagonist should be related to the magnitude of the unwanted effects, especially in the CNS and cardiovascular system, and a benefit-risk ratio or therapeutic index should be developed for each medication in this class (Simons, 1994).

The investigation of the efficacy of plant based drugs used in the traditional medicine have been paid great attention because they are cheap, have little side effects and according to WHO still about 80% of the world population rely mainly on plant-based drugs (Kumara, 2001). There are few review papers on medicinal plants for their inhibitory effect on histamine (H_1) receptors. Different research studies show that there are many reports on anti-histaminic effects of various medicinal plants. In this review, the inhibitory effects of extracts, some fractions and some constituents of medicinal plants on histamine (H_1) receptors were reviewed.

Method

Online literature searches were performed using Medline, PubMed, Science Direct, Scopus, and Google Scholar websites from 1974 to 2016 to identify studies about effects of medicinal plants on histamine (H_1) receptors. The keywords used for searching were; medicinal plant, histamine (H_1) receptors, relaxant effect.

Inhibitory effect of medicinal plants on histamine (H_1) receptors

Nigella sativa

Nigella sativa (N. sativa) also known as black cumin from Ranunculaceae family is an annual flowering plant with green to blue flowers and small black seeds, which grows in south and southwest Asia. The seeds of *N. sativa* contain thymoquinone, monotropens such as pcymene and α-pinene (Gad et al., 1963), Nigellidine and Nigellimine (Malik et al., 1995) and a saponin (Ansari & Sadiy, 1989). In traditional medicine, *N. sativa* is recommended for various diseases such as fever, cough, bronchitis, asthma, chronic headache, migraine, dizziness, chest congestion, dysmenorrhea, obesity, diabetes, paralysis, hemiplegia, back pain, infection, inflammation, rheumatism, hypertension, and gastrointestinal problems such as dyspepsia, flatulence, dysentery, and diarrhea (Ansari & Satish, 2013). Different therapeutic effects have been described for *N. sativa* such as anti-asthma and anti-dyspnea (Boskabady et al., 2007b), anti-tussive (Boskabady et al., 2015), anti-inflammatory and immunomodulatory (Salem, 2005). It was indicated that the volatile oil of *N. sativa* protected guinea pigs against histamine-induced bronchospasm, but in isolated tissues it did not affect histamine (H_1) receptors (Mahfouz & El-Dakhakhny, 1960). The inhibitory effect of *N. sativa* on histamine (H_1) receptors of tracheal smooth muscle was also examined using concentration-response curve to histamine. Findings demonstrated that plant led a parallel rightward shift in histamine concentration-response curve which was similar to that of chlorpheniramine. The maximum response to histamine was also obtained in the presence of the plant extract. The values of the concentration ratio minus one (CR-1) produced by the macerated extract was also significantly greater than that of chlorpheniramine, showing a higher competitive antagonistic effect of this extract than that of chlorpheniramine on histamine (H_1) receptors at used concentrations (Boskabady & Sheiravi, 2002).

Rosa damascene

Rosa damascena (R. damascena), commonly known as Damask rose or sometimes as the rose of Castile, is an ornamental plant from the Rosaceae family which grows 2.2 meters in height (Kaul et al., 2000). This plant contains flavonoids such as caempferol and quercetin and their glycoside derivatives (Schieber et al., 2005), carboxylic acid (Green, 1999), terpene, myrcene (Babulka, 2007), and vitamin C (Libster, 2002). Several pharmacological effects have been described for this plant such as anti-inflammatory (Hajhashemi et al., 2010), anti-tussive (Shafei et al., 2010), anti-spasmodic (Rasheed et al., 2015), antioxidant activity (Yassa et al., 2015) and anti-bacterial (Basim & Basim, 2003).

The relaxant effects of ethanolic extract and essential oil of this plant on tracheal smooth muscle was also documented. The possible mechanism of this effect was investigated by its effect on methacholine-induced contraction in non-incubated and incubated (with propranolol and chlorpheniramine) tissues. Findings showed that the relaxant effect of *R. damascena* was almost completely inhibited in incubated tissues which propose a possible (H_1) receptor inhibitory effect for this plant (Boskabady et al., 2006a).

Thymus vulgaris

Thymus vulgaris (T. vulgaris) is a flowering plant which belongs to the lamiaceae family. It is a bushy, woody-based evergreen subshrub with small, highly aromatic, grey-green leaves and clusters of purple or pink flowers in early summer (Mansour, 2016). The essential oil of *T. vulgaris* contains thymol, p-cymene, myrcene, borneol, and linalool (Imelouane et al., 2009). Pharmacological effects of *T. vulgaris* include antiseptic, carminative, anti-microbial, anti-oxidative (Baranauskienė et al., 2003), anti-bacterial (Marino et al., 1999) and antibiotic effects (Rota et al., 2008). There is evidence of relaxant effects of this plant on tracheal and ileal smooth muscle (Meister et al., 1999).

The effect of macerated and aqueous extracts of *T. vulgaris* on guinea pig tracheal smooth muscle showed that the plant has a relatively potent relaxant effect, which was comparable with that of theophylline at used concentrations. The possible mechanism of this effect on methacholine-induced contraction in non-incubated and incubated (with propranolol and chlorpheniramine) tissues were evaluated. The results suggested a possible inhibitory effect of the plant on H_1receptors of guinea pig trachea smooth muscle (Boskabady et al., 2006b).

Carum copticum

Carum copticum (C. copticum) commonly known as "Ajwain" is a perennial plant with white flowers and small brownish seeds which grows in Iran and India, states of Gujarat and Rajasthan. The seeds of this plant contain terpinene, p-cymene, α-pinene, β-pinene and other substances such as thymol and carvacrol (Shankaracharya et al., 2000). Therapeutic uses of *C. copticum* seeds include anti-vomiting, analgesic, anti-asthma and anti-dyspnea effects (Avicenna, 2014), anti-microbial and anti-viral activities (Oskuee et al., 2011) and relaxant effect (Boskabady et al., 2003).

The inhibitory effect of *C. copticum* on histamine (H_1) receptors of guinea pig tracheal smooth muscle was also evaluated using concentration-response curve to histamine and the results indicated a competitive antagonism effect of the plant on histamine (H_1) receptors (Boskabady & Shaikhi, 2000).

Zataria multiflora

Zataria multiflora (Z. multiflora) is a flowering plant in the Lamiaceae family with a woody, fibrous root which grows in Iran, Afghanistan, Pakistan, and Kashmir. Main components of *Z. multiflora* essential oil are terpenes, phenols, thymol, carvacrol, terpenoids, aliphatic alcohols and flavonoids (Sajed et al., 2013). This plant has several therapeutic effects including in anti-bacterial (Motevasel et al., 2011) anti-inflammatory, analgesic (Hosseinzadeh et al., 2000) antioxidant (Sharififar et

al., 2007) and spasmolytic properties (Sajed et al., 2013). The relaxant effect of *Z. multiflora* in ileum (Naseri, 2003), uterus (Gharib Naseri et al., 2010) and tracheal smooth muscle have been demonstrated (Boskabady et al., 2009).

The inhibitory effect of aqueous-ethanolic extract of *Z. multiflora* and carvacrol, a major constituent of *N. sativa*, *C. copticum*, and *Z. multiflora* on histamine (H_1) receptor of guinea pig tracheal smooth muscle was also reported using concentration-response curve to histamine (Boskabady & Tabanfar, 2011; Boskabady et al., 2012).

Crocus sativus

Crocus sativus (C. sativus) or saffron is a flowering plant belonging to the Iridaceae family which is widely cultivated in Iran and some other countries. The main components of *C. sativus* are crocins, safranal, picrocrocin, ketoisophorone, isophorone, glycosidic terpenoids and crocetin (Tarantilis et al., 1995). This plant is an important medicinal plant and it has been used for its anti-inflammatory (Mahmoudabady et al., 2013), anti-tussive (Hosseinzadeh & Ghenaati, 2006) antioxidant (Papandreou et al., 2006), anti-diabetic (Mohajeri et al., 2008), anxiolytic and hypnotic (Hosseinzadeh & Noraei, 2009) and antidepressant effects (Hosseinzadeh et al., 2003).

The relaxant effect of *C. sativus* on guinea pig tracheal smooth muscle was examined by its effect on KCl-induced contraction in non-incubated and incubated (with atropine, propranolol and chlorpheniramine) tissues. The results showed that the relaxant effect of the plant in incubated tissues were non-significantly higher than its effect in non-incubated tissues which suggests a possible inhibitory effect on histamine (H_1) receptors of guinea pig tracheal smooth muscle (Boskabady & Aslani, 2006). In addition, the inhibitory effect of hydro-ethanolic extracts of *C. sativus* and its constituent, safranal on guinea pig tracheal smooth muscle was also demonstrated (Boskabady et al., 2010; Boskabady et al., 2011).

Portulaca oleracea

Portulaca oleracea (P. oleracea) is an annual plant which belongs in the family Portulacaceae which may reach 40 cm in height. The main active constituents of *P. oleracea* include: noradrenaline, calcium salts, dopamine, malic acid, citric acid, glutamic acid, asparagic acid, nicotinic acid, alanine, glucose, fructose, and sucrose (Michael, 1988). Several pharmacological effects for this plant such as bronchodilatory (Malek et al., 2004), anti-tussive (Boroushaki et al., 2010), antioxidant (Dkhil et al., 2011), analgesic and anti-inflammatory activities (Chan et al., 2000) were reported.

The effect of boiled and aqueaus extracts of *P. oleracea* on tracheal smooth muscle was examined by methacholine-induced contraction in non-incubated and incubated (with propranolol and chlorpheniramine) tissues. Findings showed that the relaxant effects of the plant in incubated tissues were lower than in non-incubated tissues which propose a possible inhibitory effect on histamine (H_1) receptors (Boskabady et al., 2004).

Bunium persicum

Bunium persicum (B. persicum) is an erect, herbaceous perennial plant in the Apiaceae family which grows in Iran, Tajikistan, Afghanistan, Pakistan and the western part of Northern India. The main constituents of *B. persicum* are p-Mentha-1, 4-dien-7-al, gamma-terpinene, beta-pinene and cuminaldehyde (Foroumadi et al., 2002). Different therapeutic effects have been described for this plant such as antimicrobial activity (Syed & Hanif, 1985), antifungal activity (Sardari et al., 1998), antinociceptive and anti-inflammatory activities (Hajhashemi et al., 2011), antioxidant activity (Shahsavari et al., 2008) and relaxant effect (Boskabady & Talebi, 1999).

The inhibitory effect of essential oil, aqueous and macerated extracts of *B. persicum* on histamine (H_1) receptor of guinea pig tracheal smooth muscle was also reported using concentration-response curve to histamine (Boskabady & Moghaddas, 2004).

Satureja hortensis

Satureja hortensis (S. hortensis) is a perennial, semi-evergreen herb in the family Lamiaceae. The main components of *S. hortensis* essential oil are Thymol, p-cymene, γ-terpinene and carvacrol (Mahboubi & Kazempour, 2011). Several therapeutic effects have been described for *S .hortensis* include antispasmodic and anti-diarrheal (Hajhashemi et al., 2000), antibacterial, antifungal, and antioxidant (Güllüce et al., 2003), antinociceptive and anti-inflammatory (Hajhashemi et al., 2002).

The relaxant effect of aqueous-ethanolic extract of the leaves of *S. hortensis* on guinea pig tracheal smooth muscle was investigated and the results indicated a potent relaxant effect for *S. hortensis* which was comparable with that of theophylline at used concentrations. The possible mechanism of this effect was evaluated by its effect on KCl-induced contraction in non-incubated and incubated (with atropine, propranolol and chlorpheniramine tissues). The results showed that the relaxant effect of the plant was almost completely inhibited in incubated tissues which suggest a possible (H_1) receptor inhibitory effect for the plant (Boskabady et al., 2007a).

Ephedra sinica

Ephedra sinica (E. sinica) also known as Ma Huang, is an evergreen Shrub native to Mongolia, Russia, and northeastern China from Ephedraceae family. Different therapeutic effects have been described for the *E. sinica* such as Antimicrobial, antifungal and antioxidant (Parsaeimehr et al., 2010), Antiviral (Yamada et al., 2008), anti-inflammatory (Yeom et al., 2006), and anti-asthma activities (Shakeri & Boskabady, 2015).

The relaxant effect of *E. sinica* on tracheal smooth muscle and its possible mechanism was examined by its effect on carbachol and histamine induced contraction. The findings suggested a possible inhibitory effect on histamine (H_1) receptors (Chu et al., 2006).

The effect of ephedrine on tracheal smooth muscles in dog and guinea pig showed that ephedrine reduced the basal tension and inhibited histamine-evoked responses, also elicited substantial hyperpolarization of the smooth muscle membrane (Bilcikova et al., 1987).

The inhibitory effect of optical isomer of methylephedrine (one of the ephedra alkaloids) on histamine (H_1) receptor of guinea pig tracheal smooth muscle was also reported (Koike et al., 1996).

Humulus lupulus

Humulus lupulus (H. lupulus) is a pharmaceutical herb strongly grown in Europe, Asia, and North America (Reeves & Richards, 2010). In traditional medicine, hop is mostly used to treat the symptoms of anxiety such as nervousness, over excitability, restlessness, and insomnia (Di Viesti et al., 2011). Hops are composed of flavonoids, phenolic acids, and terpenophenolics (Kavalier et al., 2011). The most important hop flavonoids are prenylflavonoids and xanthohumol (Chen et al., 2012). Various therapeutic effects including analgesic (Hejazian & Mahdavi, 2007), estrogenic (Chadwick et al., 2006) and sedative (Dimpfel & Suter, 2008) have been shown for hop.

It also enhances the gastric secretions by stimulating the enteric cholinergic neurons (Kurasawa et al., 2005). Thus, the spasmolytic effect of hops extract on rat's ileum may be in part due to the activation of these receptors which are among the inhibitory mediators of intestinal smooth muscle contraction (Akamatsu et al., 2007). The inhibitory effect of *H. lupulus* on histamine receptor of rat ileum was demonstrated. Even so, the involvement of GABAergic systems, calcium influx, or any other possible mechanisms in relaxant effects of hops extract on rat's illeal contraction should be further investigated.

Combretum racemosum

Combretum racemosum (C. racemosum) is a climbing shrub and inhabitants of the eastern parts of Nigeria use its leaves in traditional medicine for the treatment of ulcers, diarrhoea, cholera and menorrhagia. The anti-ulcer effects of *C. racemosum* in various experimental ulcer models have been evaluated in rats (Okwuosa et al., 2006).

The raw methanolic extract of *C. racemosum* possesses gastric anti-secretory activities due to possibly inhibition of calcium mobilization and H_2 receptor antagonistic potency which may be due to single or combined effect (s) of the phytochemical constituents (Okwuosa et al.).

Aegle marmelos

Aegle marmelos (A. marmelos) commonly known as bael, is one of the most important medicinal plants of India, Burma and Ceylon (Srivastva et al., 1996). Different chemical constituents like alkaloids, coumarins and steroids have been isolated and identified from different parts of the tree. This plant is used in traditional medicine treatments, such as intermittent fever, intestinal ailments, fertility control and treatment after childbirth and fish poison (Basu & Sen, 1974). The alcoholic extract of Bael leaves, containing Lupeol and Citral antagonized the histamine–induced contractions and demonstrated positive relaxant effect in isolated guinea pig ileum and tracheal chain, suggesting inhibition of H_1-receptor activity (Arul et al., 2004) and act through inhibition of histamine mediated signaling (Geetha & Varalakshmi, 2001) and relaxant effect in isolated guinea pig ileum and tracheal.

Ginkgo biloba

Ginkgo biloba leaf (G. biloba) has been widely reported to have a protective effect against subarachnoid hemorrhage (Sun et al., 2003). *Sophora japonica L.* flower bud (*S. japonica*) has been recorded as a remedy for cerebral hemorrhage. Nguyen et al. have shown that *S. japonica* and *G. biloba* exert inhibitory effects on the vasoconstriction induced by various agents. The effects of *S. japonica* and *G. biloba* are attributed to antagonism of the H_1, 5-HT2 and TXA2/PG receptors, and provide an explanation for their therapeutic use for cerebral disorders (Nguyen et al., 2016).

Eriobotrya japonica

The leaves of *Eriobotrya japonica (E. japonica)* are ethno pharmacologically used to treat diarrhea, asthma and hypertension in Zimbabwe. The results suggest that the ethanolic leaf extract of *E. japonica* has myorelaxant effects and may be acting by potentially inhibiting acetylcholine, histamine and potassium receptors on the rabbit ileum (Matimba et al.).

Conclusion

In this review article the inhibitory effect of some medicinal plants on histamine (H_1) receptors in various types of smooth muscles including tracheal, vascular and gastro-intestinal and urogenital were discussed. Several medicinal plants including *Nigella sativa, Rosa damascena, Thymus vulgaris, Carum copticom, Zataria multiflora, Crocus sativus, Portulaca oleraceae, Bunium persicum, Satureja hortensis, Ephedra sinica, Humulus lupulus, Combretum racemosum, Aegle marmelos, Ginkgo biloba and Eriobotrya japonica* showed relaxant effect on various types of smooth muscle. These plants also showed competitive antagonism effect on histamine (H_1) receptors which could be contribute in their smooth muscle relaxant effect. However, further clinical and experimental studies were required to demonstrate the exact mechanism of action and the clinical applications of this effect more clearly.

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