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Review Article

Medicinal Plants and Histamine (H_1) Receptors: An Updated Review

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Abstract

Background: Histamine (H_1) receptors play vital roles in a variety of physiological and pathological processes, including allergic reactions, inflammation, immunological responses, bronchoconstriction, pain, and memory deficit. Traditional medicine recognizes the therapeutic potential of medicinal plants in treating these conditions. This comprehensive review attempts to provide detailed information about the effects of medicinal plants on H_1 receptors.

Methods: The modulatory effects of several medicinal plants, including *Achillea millefolium*, *Berberis vulgaris*, *Bunium persicum*, *Carum copticum*, *Crocus sativus*, *Curcuma longa*, *Ferula assafoetida*, *Garcinia mangostana*, *Ginkgo biloba*, *Nigella sativa*, *Portulaca oleracea*, *Rosa damascena*, *Silybum marianum*, and *Zataria multiflora*, on H_1 receptor activity and signaling pathways were investigated by searching PubMed, Scopus, and Google Scholar from inception until March 2024.

Results: According to the findings, various plant extracts or their main components blocked H_1 receptors in some neurons of the nervous system and smooth muscles in the trachea and arteries. The therapeutic properties of these plants may be considered in treating allergies and asthma by blocking H_1 receptors, relaxing smooth muscles, and decreasing the levels of inflammatory cytokines. They may also help alleviate pain by decreasing pain response, improve memory deficit through H_1 receptor antagonism, reduce working memory errors, and treat insomnia by binding to H_1 receptors and increasing sleep duration.

Conclusion: In conclusion, the mentioned herbs block H_1 receptors and may be potential candidates for treating allergies, asthma, pain, insomnia, and memory deficit. However, further research is needed to determine their efficacy in humans.

Introduction

Histamine, a biogenic amine, is an important signaling molecule involved in several physiological and pathological processes in the human body. It exerts its effect by interacting with four distinct receptor subtypes: H_1, H_2, H_3, and H_4. The H_1 receptor is one of these subtypes that has attracted substantial research due to its role in allergic reactions and its association with a variety of clinical disorders.[1] The H_1 receptor is found in various tissues and cell types, such as adrenal medulla, chondrocytes, dendritic cells, endothelial cells, liver cells, lymphocytes, muscle cells, nerve cells, respiratory epithelial cells, and vascular smooth muscle cells.[2,3] The modulation of H_1 receptors is particularly significant, as it directly influences the pathophysiology of allergic responses,[4] inflammation,[5] and other histamine-mediated conditions, making it a critical target for therapeutic intervention.[3]

In general, the H_1 receptor is primarily associated with the Gq protein, which activates phospholipase C to raise inositol phosphates and intracellular calcium levels; the H_2 receptor interacts with the Gs protein, which stimulates cyclic adenosine monophosphate (cAMP) synthesis; and the H_3 receptor and H_4 receptor signal through the Gi/o proteins.[6]

Smooth muscle cells, endothelial cells, and immune cells are the most common sites of H_1 receptor expression.[7] Activation of H_1 receptors causes a variety of cellular responses, including increased vascular permeability, vasodilation, bronchoconstriction, pruritus, and the production of pro-inflammatory mediators such as histamine, leukotrienes, and prostaglandins.[8,9] These reactions help to develop allergic disorders, including allergic rhinitis, asthma, and atopic dermatitis.[2] Considering the prevalence of these conditions, effective modulation of H_1 receptors is essential for improving

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patient outcomes and quality of life.

The H_2 receptor, located largely in gastric parietal cells, controls stomach acid secretion. The activation of H_2 receptors enhances the synthesis of cAMP, which increases acid secretion. Consequently, H_2 receptor antagonists are used in the treatment of stomach ulcers and gastroesophageal reflux disease (GERD).[10] The H_3 receptor is mostly located in the central nervous system (CNS) and functions as both an autoreceptor and a heteroreceptor.[11] It controls histamine production and release, as well as the release of other neurotransmitters, including dopamine, norepinephrine, and serotonin.[12] Modulation of H_3 receptors has disclosed possibilities in the treatment of cognitive disorders such as Alzheimer's disease and attention deficit hyperactivity disorder (ADHD).[13] The H_4 receptor, which is largely expressed on immune cells, regulates inflammatory responses and immune cell chemotaxis. Activation of H_4 receptors stimulates the production of pro-inflammatory cytokines and chemokines, as well as attracting immune cells to the site of inflammation. Modulating H_4 receptors has emerged as an appealing therapy for allergy and inflammatory diseases.[2,14]

It is essential to note that histamine, mostly mediated by H_1 receptors, plays a crucial role in allergy and anaphylaxis.[15] Antihistamines have been used for allergic diseases since the early 1950s, and for more than 50 years, they have been the first line of treatment for many allergic disorders, including hay fever, allergic rhinitis, and urticarial.[1] Due to their limited receptor selectivity and easy blood-brain barrier penetration, early antihistamines have a number of serious adverse effects, including dry mouth, arrhythmia, and sedation.[16,17] Subsequent additions of the carboxyl moiety and protonated amine enhance receptor selectivity and greatly lessen brain permeability-related negative effects. But even second- or third-generation antihistamines, such as loratadine (Claritin), fexofenadine (Allegra), and cetirizine (Zyrtec), still have some unfavorable side effects, like headache, sleepiness, and dizziness.[1,18] This underscores the urgent need for alternative therapeutic strategies that can effectively target H_1 receptors with fewer side effects.

Medicinal plants have long been used to treat histamine-related disorders. These plants include a wide variety of bioactive compounds that can influence H_1 receptor activity and histamine-mediated processes.[19,20] Multiple mechanisms affect the physiological effects of medicinal plants on H_1 receptors. Some herbs act as H_1 receptor antagonists, which prevent histamine binding and subsequent downstream signaling.[21] The therapeutic potential of these herbal medicines is significant, as they may offer safe and effective alternatives or complementary options to conventional antihistamines.[22-24]

Despite the traditional use and anecdotal evidence supporting the efficacy of medicinal herbs in histamine-related disorders, there remains a critical need for a comprehensive understanding of their effects on H_1 receptors and the underlying molecular mechanisms. This research is significant not only for advancing the knowledge of herbal medicine but also for identifying novel therapeutic agents that can improve the management of histamine-mediated conditions. By elucidating the mechanisms of action and therapeutic applications of medicinal herbs on H_1 receptors, this study aims to contribute to the growing body of evidence supporting their use as natural alternatives or complementary agents in the treatment of allergic and inflammatory disorders. It is worth noting that a research team has previously published a related article on the effects of some medicinal plants on histamine (H_1) receptors.[21] This review seeks to integrate the available scientific literature, expanding upon previous work by including recent studies, additional medicinal plants, and incorporating figures and tables to enhance the depth and clarity of the analysis. By doing so, our team aims to provide a comprehensive resource that highlights the importance of H_1 receptor modulation by herbal medicines and their potential to transform the landscape of treatment for histamine-related disorders.

Methods

A comprehensive literature search was carried out using several online databases such as PubMed, Scopus, and Google Scholar to find relevant research studying the effects of medicinal plants on H_1 receptors. The search covered items from the inception of these databases until March 2024. The following MeSH terms from the title and abstract were used to establish the search strategy: "histamine (H_1) receptor", "herbal medicine", "medicinal plant", "smooth muscle", "asthma", "allergy", "nervous system", "vessels", "arteries", "animal", "human", "*in vivo*", and "*in vitro*".

Data collection method: The data collection involved reviewing the identified articles to extract relevant information regarding the effects of medicinal plants on H_1 receptors. This included analyzing the methodologies, results, and conclusions of the studies that met the inclusion criteria.

Inclusion criteria: Studies were included if they met the following criteria: (1) they investigated the effects of herbal medicines or medicinal plants on H_1 receptors; (2) they involved either *in vitro* experiments or animal and human subjects; and (3) the manuscripts were peer-reviewed and published in English (at least the abstract).

Exclusion criteria: Review articles, abstracts from congresses or symposiums, and studies that did not specifically address the effects of medicinal plants on H_1 receptors were excluded from the analysis. Additionally, studies that focused solely on H_2, H_3, or H_4 receptors without mentioning H_1 receptors were also excluded.

Typically, the effect of medicinal herbs on histamine H_1 receptors *in vitro* is evaluated using three typical strategies. Initially, the effects of medicinal plants, fractions, and components on non-incubated and incubated tissue are investigated using a pharmacological H_1 receptor

competitive antagonist such as chlorpheniramine. The reduction in associated effect in incubated tissues with the competitive antagonist suggests a possible inhibitory effect on H_1 receptors. Some studies only examine the effects of a single concentration of extracts, fractions, or components, whilst others assess several concentrations, including determining the effective concentration that induces a 50% maximum response (EC_{50}).

Another method involves conducting concentration-response curves to acetylcholine or isoprenaline in the presence and absence of extracts, fractions, or components of medicinal plants on non-incubated and incubated tracheal smooth muscle (TSM) with a pharmacological H_1 receptor antagonist. The decrease in maximum response and EC_{50}, as well as a parallel shift in the concentration-response curve in tissues incubated with the H_1 receptor antagonist, indicates an H_1 inhibitory activity.

The third approach involves performing concentration-response curves using a pharmacological H_1 receptor agonist (such as histamine) in the presence and absence of medicinal plant extracts, fractions, or components. In that method, the presence of extracts, fractions, or components causes a rightward shift in the cumulative concentration-response curves and an increase in EC_{50} for histamine, showing that they block H_1 receptors. Furthermore, repeating the concentration-response curve with an H_1 agonist in the presence of an H_1 competitive antagonist improves clarity by shifting the agonist response curve to the right. This method is regarded as the most exact pharmacological strategy for determining the inhibitory effect of an agent on H_1 receptors.

In contrast, assessing the effects of medicinal plants on H_1 receptors *in vivo* requires (a) administering plant extracts or components and measuring the response, (b) administering an H_1 antagonist to animals ahead of treatment, and (c) repeating the administration of plant extracts or components and evaluating any changes in the corresponding response.

Exploring the modulatory influence of medicinal plants on histamine (H_1) receptors

Achillea millefolium

Achillea is a genus within the Asteraceae family, and it is found in various regions, including Iran. *A. millefolium*, a species within this genus, has been associated with a range of pharmacological effects. These effects include antihemorrhagic, antihypertensive, anti-inflammatory, antioxidant, antimicrobial, antispasmodic, astringent, bronchodilatory, diuretic, and urinary antiseptic properties effects.[25] *A. millefolium* is rich in phytochemicals, primarily consisting of essential oils and a variety of flavonoids. Key compounds include apigenin, camphor, lutein, and rutin, with the essential oil mainly made up of monoterpenes and sesquiterpenes. Additionally, the plant features other flavonoids such as morin, myricetin, naringin, and naringenin, along with distinctive compounds like millifolide A, B, and C, 3-methoxytanapartholide, seco-tanapartholide A, and achillinin A. This diverse array of flavonoids also encompasses aglycones, flavones, and flavonol O-glycosides, further enhancing the plant's complex phytochemical profile.[26]

Achillea millefolium extract

Respiratory system

To investigate a potential mechanism underlying the relaxant effect of *A. millefolium*, an aqueous-ethanolic extract was tested on methacholine concentration-response curves under three experimental conditions: non-incubated TSM (group 1), TSM incubated with propranolol and chlorpheniramine (group 2), and tissue incubated with propranolol alone (group 3). In groups 2 and 3, the EC_{50} values obtained with all extract concentrations were considerably greater than saline. Furthermore, when compared to groups 1 and 3, group 2 had considerably higher EC_{50} values for all extract concentrations. However, only the higher concentration of the extract resulted in substantially reduced maximum responses to methacholine compared to saline in group 1. The slopes of the methacholine-response curves did not change substantially between the various extract concentrations, saline, or the three groups. In the first group, all extract concentrations had considerably lower concentration ratio minus one (CR-1) values than atropine, although there were no significant differences in the other groups. Conversely, in groups 2, CR-1 values obtained with all extract concentrations were considerably higher than in groups 1 and 3. Based on these observations, it was suggested that the extract could demonstrate an inhibition of histamine (H_1) receptors[27] (Table 1).

It is important to note that further research is required to elucidate the detailed mechanisms involved and to gain a deeper understanding of the pharmacological effects of the extract. Nonetheless, these results provide evidence supporting the potential histamine receptor-blocking properties of the *A. millefolium* extract.

Berberis vulgaris

Berberis vulgaris L., commonly referred to as barberry, belongs to the Berberidaceae family. It is native to central and southern Europe, northwest Africa, and western Asia, specifically Iran. This shrub can reach a height of 1-3 meters and has thorny yellow wood as well as sour red fruits. Extensive phytochemical investigation has confirmed the presence of a number of compounds in *B. vulgaris*, including carbohydrates, alkaloids, glycosides, amino acids, proteins, flavonoids, saponins, and tannins. Berberine is the most prominent of these components. Traditional Iranian medicine extensively recognizes the therapeutic properties of *B. vulgaris*. These include tonic, antimicrobial, antiemetic, antipyretic, antipruritic, and coagulant effects.[37] Recent scientific research has shed light on the pharmacological properties of *B. vulgaris*, unveiling its antioxidant,[38] antimicrobial[39] anti-

Table 1. The effects of *A. millefolium*, *B. vulgaris*, *B. persicum*, *C. copticum*, *C. sativus* and their main components on histamine (H_1) receptors

Herb/Compound	Type of used tissue	Doses	Results	Ref.
A. millefolium AEE	Guinea pigs TSM	0.2, 0.4, 0.8 mg/mL	TSM relaxation H_1 inhibitory effect	27
Berberine	Rat TSM	20, 65, 200, 600 µg/mL	Concentration-dependent TSM relaxation Blocked H_1 receptors	28
B. persicum AME, EO	Guinea pigs TSM	AME: 0.08 mL EO: 3 µL	TSM relaxation H_1 receptor inhibition	29
C. copticum EO, AMEE	Guinea pigs TSM		TSM relaxation H_1 inhibitory effect	30
C. copticum EO, AMEE	Guinea pigs TSM	EO: 0.5 mL AMEE: 0.03 mL;	TSM relaxation Possible H_1 inhibition	31
C. sativus AEE and safranal	Guinea pigs TSM	AEE: 0.15, 0.3, 0.45, and 0.60 g % Safranal: 0.15-0.60 mg/mL	TSM relaxation Possible H_1 receptor inhibitory effect	32
C. sativus AEE and safranal	Guinea pigs TSM	AEE: 0.1 and 0.2 g% Safranal: 1.25 and 2.5 µg	Possible H_1 receptor inhibitory effect	33
C. sativus AEE	Guinea pigs TSM	0.025, 0.05, 0.1 g%	Inhibited H_1 receptors	34
Safranal	Guinea pigs TSM	0.63, 1.25, 2.5 µg/mL	Antagonistic effect on H_1 receptors	35
Crocin	Rat TSM	30, 60, 120 µM	TSM relaxation No significant effect on H_1 receptors	36

AEE: aqueous-ethanolic extract; AME: aqueous, macerated extract; EO: essential oil, COX-2: cyclooxygenase-2; TSM: tracheal smooth muscle.

inflammatory, immunomodulatory,[40] antihypertensive,[41] and antihistaminic[42] effects.

Berberis vulgaris main components

Respiratory system

The relaxant effect of berberine was evaluated on rat TSM. The results showed considerable and concentration-dependent relaxant effects of berberine on contracted tissues. EC_{50} values of berberine were considerably greater in tissues incubated with chlorpheniramine compared to those of non-incubated tissues. Based on these data, the study concludes that berberine has a moderately significant relaxant effect on rat TSM, but less than theophylline. The relaxant property of berberine was proposed to be mediated via the blocking effect of histamine H_1 receptors, inhibiting cyclooxygenase pathways, and/or producing nitric oxide[28] (Table 1).

Although the plant itself does not show inhibitory effect on H_1 receptor[37] but, its constituent berberine demonstrates this effect. More research is needed to validate these findings and investigate the clinical applications of berberine as a treatment for respiratory disorders.

Bunium persicum

Bunium persicum is a plant characterized by grassy leaves, white or pink flowers, and small brownish seeds. It predominantly grows in warm climate regions of Iran. The seeds of *B. persicum* have been attributed with various therapeutic effects, including anticonvulsant effects, gynecological benefits, diuretic properties, digestive and urinary tract disorders, and potential use in managing asthma and dyspnea. This plant also has antimicrobial and antifungal properties.[29]

Bunium persicum extract and essential oil

Respiratory system

The antihistaminic effects of aqueous and macerated extracts, as well as the essential oil of *B. persicum*, on the concentration-response curves of histamine-induced contraction in isolated guinea pig TSM were assessed. Three different experimental conditions were examined, including (1) indomethacin, (2) atropine, indomethacin, propranolol, and (3) indomethacin and propranolol incubated TSM. The results demonstrated notable rightward shifts in the histamine-response curves when the essential oil was present in groups 2 and 3, the aqueous extract in group 3, and macerated extract in group 2. These shifts were observed when comparing the curves obtained in the presence of saline. Furthermore, the EC_{50} values obtained in the presence of the essential oil, extracts, and chlorpheniramine in all three experimental sets were significantly higher compared to those obtained with saline. In terms of the maximum response, the presence of the aqueous extract in group 3 led to an improvement when compared to group 1, while the macerated extract in group 2 showed improvement compared to the other two experimental sets.[29] The findings of this study indicated an inhibitory effect of the plant on the H_1 receptor.

It is worth noting that further research is necessary to explore the specific constituents responsible for these observed effects.

Carum copticum

Carum copticum, also known as Ajwain, is a member of the Apiaceae plant family. Its seeds are widely utilized in India as a food additive and are primarily recognized for their therapeutic benefits due to their hot nature. *C. copticum* has a long history of therapeutic applications in traditional medicine. It has been found to possess anti-dyspnea, antitussive, and bronchodilatory effects.[43] Additionally, *C. copticum* has demonstrated therapeutic effects in gastrointestinal disorders such as abdominal pain, abdominal tumors, cramps, Helicobacter pylori infection, and reflux. It has also shown efficacy in treating eye infections. The seeds of *C. copticum* are

utilized for various therapeutic purposes, including anti-lithiasis, antimicrobial, antiparasitic, antiplatelet-aggregatory, antiseptic, carminative, expectorant for amoebiasis, and relief of acute pharyngitis symptoms and common cold. Furthermore, the plant has been observed to have abortifacient, diuretic, and galactogogic activities. There is also evidence suggesting its potential as an anticarcinogenic agent.[44] This plant is composed of various constituents, including carbohydrates, glucosides, phenolic compounds like carvacrol, and saponins. It also contains volatile oils such as thymol, along with beta-pinene, para-cymene, and terpenes. Additionally, it provides fats, fiber, protein, and a range of minerals, including calcium, iron, nicotinic acid (niacin), and phosphorus.[44]

Carum copticum extract and essential oil

Respiratory system

The impact of *C. copticum* extracts and essential oil on H_1 receptors of guinea pig TSM was investigated. The findings revealed noticeable rightward shifts in histamine response curves when extracts, essential oil, and chlorpheniramine were present in comparison with the saline curves. The histamine EC_{50}, in the presence of extracts, essential oil, and chlorpheniramine, were significantly higher than those of saline, with the exception of the macerated extract in group 1 (incubated with indomethacin). However, the maximum response to histamine in the presence of extracts and essential oil was lower, except for the maximum response of essential oil in group 2 (incubated with indomethacin, propranolol, and atropine). Furthermore, the maximum responses observed in the presence of extracts in group 2 experiments showed improvement compared to the other two sets of experiments. When comparing the slope of the histamine-response curves, parallel shifts were observed in curves obtained with all the extracts and essential oil in group 2 experiments.[30] These results were confirmed by another similar investigation that reported the lack of a significant difference between the EC_{50} values obtained in the presence of *C. copticum* essential oil and extracts compared to saline could potentially be attributed to the blockade of histamine H_1 receptors by the plant.[31]

The findings of this study provide valuable information into the pharmacological properties of *C. copticum* in relation to histamine H_1 receptors. The rightward shifts in the histamine response curves indicate a decrease in the sensitivity of the receptor to histamine, suggesting a competitive antagonism effect. This blocking effect could be attributed to the constituents present in *C. copticum* extracts and essential oil. The significant increase in the histamine EC_{50} values in the presence of extracts and essential oil further supports their inhibitory effects on H_1 receptors. However, it is noteworthy that the macerated extract in group 1 experiments did not show a significant difference in EC_{50} values compared to saline. This discrepancy could be attributed to variations in the composition or concentration of active compounds in the macerated extract. The lower maximum response to histamine observed in the presence of extracts and essential oil suggests a reduction in the contractile response of the guinea pig TSM. This could be beneficial in conditions such as bronchoconstriction, as *C. copticum* may attenuate the excessive contraction of the airway smooth muscles.

In brief, the results highlight the potential of *C. copticum* extracts and essential oil as competitive antagonists of histamine H_1 receptors. Further research is necessary to identify the specific active compounds responsible for these effects and explore their therapeutic advantages in respiratory conditions associated with histamine-induced bronchoconstriction.

Crocus sativus

Saffron, officially known as *Crocus sativus* L., is a member of the Iridaceae family. It normally grows to a height of 8-30 cm. *C. sativus* is most commonly found in dry regions, mainly in Iran, but also in France, Italy, Spain, and Turkey.[45] In addition to its culinary application as a food ingredient because of its distinctive color and aroma, *C. sativus* is also used as an herbal medicine. The main components of *C. sativus* include crocetin, picrocrocin, and safranal. All *C. sativus* qualities, including aroma, color, odor, and taste, rely on these components. In addition, the plant included volatile fragrance and nonvolatile active fractions, including alpha- and beta-carotenes, carotenoids, lycopene, and zeaxanthin. In folk medicine *C. sativus* has various uses, including antispasmodic, appetizer, aphrodisiac, carminative, diaphoretic, eupeptic, expectorant, flatulence, sedative, and tranquilizer.[46] It has also displayed numerous pharmacological activities such as antioxidant,[47-49] anti-inflammatory,[50,51] antiapoptotic,[52,53] anti-obesity,[54] immunomodulatory,[55,56] neuroprotective,[57,58] renoprotective,[59,60] antirheumatic,[61] and antidepressant[62] effects.

Furthermore, a number of research have examined the effect of *C. sativus* on H_1 receptors; these findings will be discussed in the next section.

Crocus sativus extract

Respiratory system

Using various methodologies, the researchers investigated the effects of aqueous-ethanolic extracts of *C. sativus* and theophylline on precontracted TSM. *C. sativus* extract showed considerable relaxant effects comparable to or even greater than theophylline on TSM precontracted with methacholine and KCl. However, when TSM were precontracted with KCl and treated with H_1 receptor antagonists, the relaxant effect of *C. sativus* extract was reduced. Therefore, the relaxant effect reported in guinea pig TSM after administering extracts of *C. sativus* might be attributed to various mechanisms, including blocking histamine H_1 receptors.[32] In another study, the stimulatory effect of *C. sativus* aqueous-ethanolic extracts

on guinea pig TSM ß-adrenoceptors were examined using cumulative concentration-response curves with isoprenaline using two concentrations of the extract, propranolol, and saline. The experiments were carried out in both non-incubated and incubated conditions with chlorpheniramine. The results showed substantial leftward changes in the isoprenaline curves when a higher concentration of the extract was applied in non-incubated tracheal chains and when both concentrations of the extract were tested in incubated TSM, relative to saline, indicating a potent stimulatory effect on β-adrenoceptors, as evidenced by a decreased EC_{50}. The extract produced lower maximal responses than saline. Negative values for the CR-1 parameter indicate stimulation of β-adrenoceptors. Furthermore, the maximum relaxant effect and EC_{50} value were different between non-incubated and incubated tissue with chlorpheniramine, indicating a potential inhibitory effect of the extract on histamine H_1 receptors.[33] The inhibitory effects of aqueous-ethanolic extracts of *C. sativus* on H_1 receptors were studied utilizing guinea pig TSM. To assess the effect on H_1 receptors, three different concentrations of the aqueous-ethanolic extract, chlorpheniramine, and saline were evaluated on three sets of guinea pig tracheal chains under the following conditions: (1) incubated trachea with indomethacin, (2) incubated trachea with indomethacin, propranolol, and atropine, and (3) incubated trachea with indomethacin and propranolol. The results revealed that the EC_{50} histamine obtained in the presence of chlorpheniramine and all extract concentrations were significantly greater than those obtained with saline, with the exception of the low extract concentration in groups 1 and 3. Furthermore, the EC_{50} values for the two higher concentrations of the extract in group 2 were higher than those in groups 1 and 3. Additionally, the maximum response obtained with the two higher concentrations of the extract in group 2 was higher than the responses recorded in groups 1 and 3. Furthermore, concentration-response curves demonstrated a parallel rightward shift when comparing the presence of only the low and medium concentrations of the extract in group 2 to those obtained with saline. These results clearly showed the effect of saffron on histamine (H_1) receptors.[34]

Crocus sativus main components

Respiratory system

Safranal on TSM contracted using methacholine and KCl indicated significant relaxant effects, which were comparable to or even greater than those of theophylline. The reported relaxation observed in guinea pig TSM after the administration of safranal could potentially be attributed to various mechanisms, such as the inhibition of histamine H_1 receptors.[32] Another investigation focused on examining the stimulating impact of safranal on β-adrenoceptors of guinea pig TSM using cumulative concentration-response curves with isoprenaline. The study employed two safranal concentrations, along with propranolol and saline. The experiments were conducted under both non-incubated and incubated TSM with chlorpheniramine. Safranal demonstrated a potent stimulating effect on β-adrenoceptors, evident from a notable decrease in the EC_{50} and negative CR-1 value. Notably, the levels of CR-1 varied significantly between propranolol and safranal. However, the maximum relaxant effect and EC_{50} value were different between non-incubated and incubated tissue with chlorpheniramine, suggesting an inhibitory effect of safranal on histamine H_1 receptors.[33] The effects of safranal at different concentrations on histamine H_1 receptors on TSM were examined by performing histamine concentration-response curves in tissues incubated with either indomethacin alone or indomethacin, propranolol, and atropine compared to saline and chlorpheniramine. The results revealed a rightward shift of histamine concentration-response curves and increased histamine EC_{50} in the presence of safranal and chlorpheniramine compared to saline. The findings suggest an inhibitory effect of safranal on histamine H_1 receptors, which is more noticeable in the group incubated with indomethacin, propranolol, and atropine.[35]

To explore the effects of crocin on histamine H_1 receptors, the relaxant effect of crocin was tested on rats' TSM incubated with chlorpheniramine and contracted with KCl. The relaxant property of crocin was found to be similar to that of non-incubated tissue. These data demonstrate that crocin does not have an inhibitory effect on histamine H_1 receptors, indicating that this mechanism is not responsible for crocin-induced TSM relaxation[36] (Table 1).

In summary, studies on *C. sativus* aqueous-ethanolic extract and its components (safranal and crocin) have shed light on their modulatory actions on TSM. Differences in the chemical composition of the extract, safranal, and crocin might be the reason for the reported differences in their effects on H_1 receptors. The extract and safranal showed competitive antagonistic actions on H_1 receptors, indicating that safranal in these plants may be responsible for the inhibitory effect of the extract on H_1 receptors. Crocin, on the other hand, did not significantly affect H_1 receptors, suggesting that its smooth muscle relaxant effect could be mediated by other mechanisms or target different receptors that are involved in muscle contraction. It is essential to note that more research is necessary to determine the exact molecular processes behind these effects and any possible interactions with other receptors.

Curcuma longa

Turmeric, scientifically known as *Curcuma longa*, is a flowering perennial herbaceous plant with rhizomes. It is a member of the Zingiberaceae family of ginger plants. It originated in India and Southeast Asia. The scientific, medicinal, and culinary fields have paid considerable attention to the roots of turmeric, which have been

used for a long time as a spice in food preparation. Although traditional medicine has long utilized *C. longa* for its medicinal properties, especially with regard to its primary component, curcumin, modern research has focused on the plant's essential components and underlying mechanisms. This herb has long been used in folk medicine to treat a wide range of diseases, such as liver problems, allergies, sinusitis, respiratory disorders, and anorexia.[63,64] Nevertheless, more recent studies have linked *C. longa* with health advantages such as anti-allergic,[65] hypoglycemic,[66] hepatoprotective,[67] hypnotic,[68] anticancer,[69] and cardioprotective[70] properties. Numerous research has also revealed that turmeric possesses anti-inflammatory,[71] immunomodulatory,[72,73] antioxidant,[74,75] anti-fibrosis,[76] and antibacterial[77] effects. Turmeric contains active compounds such as curcumin, a type of flavonoid, along with various volatile oils, including atlantone, turmerone, and zingiberone.[78]

Additionally, a variety of research studies have explored the influence of *C. longa* on H_1 receptors. These findings will be the subject of discussion in the upcoming section.

Crocus longa extract

Nervous system

A study investigated the sleep-promoting properties of an aqueous-ethanolic extract of *C. longa*. In mice, oral treatment of the extract substantially shortened sleep latency and enhanced non-rapid eye movement sleep (NREM) duration while having no effect on delta activity. Similar to doxepin, an aqueous-ethanolic extract of *C. longa* suppressed the increase in action potentials in hypothalamic neurons caused by the H_1 receptor agonist (2-pyridylethylamine dihydrochloride). In animal tests using neurotransmitter agonists or antagonists, the effects of the extract mimicked the H_1 receptor antagonistic effect of doxepin. Furthermore, both the extract and doxepin decreased sleep latency and raised NREM in wild-type mice; however, these effects were not found in H_1 receptor knockout animals[79] (Table 2).

Respiratory system

On rat TSM precontracted by methacholine or KCl, the relaxant effect of cumulative concentrations of hydro-ethanolic extract of *C. longa* was examined. The tissues were either un-incubated or were incubated with various substances, such as propranolol, diltiazem, L-NG-Nitro arginine methyl ester (L-NAME), glibenclamide, atropine, chlorpheniramine, indomethacin, and papaverine. *C. longa* demonstrated notable concentration-dependent relaxant effects on contraction caused by methacholine and KCl in non-incubated TSM. Theophylline and *C. longa* did not significantly differ from one another in their relaxant effects under contraction conditions triggered by KCl or methacholine. The extract also demonstrated strong concentration-dependent relaxant effects in tissues incubated with propranolol, diltiazem, L-NAME, and glibenclamide on methacholine-induced contraction and in tissues incubated with atropine, chlorpheniramine, indomethacin, and papaverine on KCl-induced contraction. The *C. longa* EC_{50} values in the incubated and non-incubated tissues did not differ substantially. Therefore, it may be concluded that *C. longa* had no inhibitory effect on the H_1 receptor of TSM based on the non-significant difference in the relaxant effect of the extract observed between non-incubated tissues and tissues incubated with chlorpheniramine.[85]

Crocus longa main components

Anti-allergic effect

An investigation was conducted to assess the anti-allergic inflammatory properties of curcumin and investigate its inhibitory mechanisms in mouse bone marrow-derived mast cells and a mouse model of passive systemic anaphylaxis induced by immunoglobulin E (IgE)/Ag. In bone marrow-derived mast cells, curcumin demonstrated a dose-dependent inhibition of cyclooxygenase-2 (COX-2)-dependent prostaglandin D_2 and 5-lipoxygenase-dependent leukotriene C_4 generation. Curcumin also slowed down intracellular calcium influx through activation of phospholipase Cγ1 (PLCγ1) and inhibited the phosphorylation of mitogen-activated protein kinases (MAPKs) and the nuclear factor-κB (NF-κB) pathway. Moreover, oral administration of curcumin considerably lessened IgE/Ag-induced passive systemic anaphylaxis, as demonstrated by decreased levels of serum leukotriene C_4, prostaglandin D_2, and histamine.[80]

These findings shed light on the therapeutic potential of curcumin and curcuminoids for various physiological processes. The anti-allergic and anti-inflammatory properties of curcumin in mast cells, as well as the mouse model of passive systemic anaphylaxis, suggest that it might be used to treat allergic disorders. Curcumin inhibits immunological responses through numerous pathways, including COX-2, leukotriene C_4, calcium influx, MAPKs, and the NF-κB pathway.

Nervous system

Molecular docking studies, histamine H_1 receptor binding assays, and experiments with H_1 receptor knockout mice revealed that curcuminoids (bisdemethoxycurcumin, demethoxycurcumin, and curcumin) significantly reduced sleep latency and increased sleep duration in mice subjected to the pentobarbital-induced sleep test. Notably, curcuminoids boosted NREM duration while not changing REM or delta activity. The findings of molecular modeling revealed that curcumin, demethoxycurcumin, and bisdemethoxycurcumin may interact with the H_1 receptor. This was reinforced further by the binding affinity experiment, which showed that curcuminoids bind strongly to the H_1 receptor. Furthermore, administering curcuminoids decreased sleep latency and enhanced NREM frequency in wild-type mice but not in H_1 receptor knockout animals.[81]

In terms of sleep-promoting properties, an aqueous-

Table 2. The effects of *C. longa*, *F. assafoetida*, *G. mangostana*, and their main components on histamine (H_1) receptors

Herb/ Compound	Type of used cells, animals, and tissues	Doses	Results	Ref.
C. longa AEE	H_1 receptor knockout mice brain slices	10 µg/mL	H_1 receptor antagonistic effect	79
	ICR and C57BL/6N mice	10–100 mg/kg, p.o.	↑Sleep duration, NREMS ↓Sleep latency	
Curcumin	BMDMC of C57BL/6 mice	1, 5, 10 µM	Activated PLCγ1, MAPKs phosphorylation, NF-κB pathway ↓ COX-2 levels	80
	ICR mice	25, 50 mg/kg, p.o.	H1 receptor antagonism ↓ IgE/Ag-induced passive systemic anaphylaxis	
Curcuminoids	Mice		H_1 receptor binding ↑Sleep duration, NREMS ↓Sleep latency	81
F. assafoetida AE	Guinea pigs TSM	2.5, 5, 10 mg/mL	TSM relaxation H_1 receptor Inhibition	82
G. mangostana fruit ME, α-mangostin	VSMC		Competitive H_1 receptor antagonist	83
	Isolated rabbit aorta		Histamine and serotonin induced contraction inhibition	
α-mangostin	Rabbit thoracic aorta and guinea-pig trachea	1.5×10^{-5} M	-Prevented histamine-induced contractions reversed by chlorpheniramine	84

AEE: aqueous-ethanolic extract; AE: aqueous extract; ME: methanolic extract; VSMC: vascular smooth muscle Cells; BMDMC: bone marrow derived mast cells IgE/Ag immunoglobulin E/antigen; MAPKs: mitogen-activated protein kinases; NF-κB: nuclear factor-κB; NREM: non-rapid eye movement sleep; PLCγ1: phospholipase Cγ1; Ref: reference; REM: rapid eye movement; Ref: reference; TSM: tracheal smooth muscle.

ethanolic extract of *C. longa* containing curcuminoids has shown promise in lowering sleep latency and increasing NREM sleep duration. The involvement of curcuminoids in histaminergic signaling is evidenced by their regulation of the H_1 receptor pathway, which is similar to the effect of doxepin. Molecular docking studies, binding affinity assays, and investigations with H_1 receptor knockout animals all support the association between curcuminoids and the H_1 receptor, highlighting their potential as sleep-promoting medications. It is important to note the limitations of these investigations. First, the studies were mostly done in animal models, and further study is needed to assess the effects in humans. Furthermore, the particular mechanisms behind the effects of curcumin and curcuminoids on mast cells, sleep control, and H_1 receptor signaling must be further investigated. Also, the bioavailability and pharmacokinetics of curcumin and curcuminoids should be addressed when determining their medicinal application. Despite these limitations, the findings of these studies reinforce the growing body of evidence supporting curcumin and curcuminoids diverse biological properties, emphasizing their potential for future therapeutic developments in allergic disorders and sleep-related conditions. More research and clinical trials are needed to completely understand their efficacy, safety, and optimal use in human populations.

Respiratory system

The effects of curcumin on TSM were investigated in non-incubated and incubated tissues with atropine, chlorpheniramine, indomethacin, and papaverine. TSM was contracted with KCl or methacholine, and cumulative amounts of curcumin or theophylline (positive control) were added to the organ bath. Curcumin demonstrated concentration-dependent relaxant effects on KCl-induced contraction in non-incubated TSM. When compared to non-incubated TSM, the relaxant effects of curcumin were notably less in tissue that was exposed to atropine. Between tissues that had been treated with atropine and those that had not, a notable change in EC_{50} was seen. In a concentration-dependent manner, theophylline had a strong relaxing effect on contractions generated by both KCl and methacholine. Moreover, the relaxant effect was tested on chlorpheniramine-incubated TSM constricted by KCl to investigate the role of H_1 receptors and the effects of curcumin on them. The data revealed that the relaxant effect of curcumin was not substantially different between incubated and non-incubated TSM. These findings demonstrated that curcumin is not a histamine H_1 antagonist and has no inhibitory effects on histamine H_1 receptors on TSM.[86]

Ferula assafoetida

The plant Asafoetida (*Ferula assafoetida*) belongs to the Apiaceae family and is well-known for its gum-resin, which is extracted from tap roots or underground rhizomes. *F. asafoetida* has been used for a number of ailments in traditional medicine, such as intestinal parasites, asthma, influenza, stomachaches, and flatulence. It is also thought to have sedative, diuretic, and aphrodisiac properties. *F. asafoetida* has also shown a number of pharmacological properties, including anti-diabetic, anti-spasmodic, antiviral, antifungal, antioxidant, and hypotensive effects.[82] Moreover, the plant's main components include α-bisabolol, carvacrol, (E)-1-propenyl-sec-butyl-disulfide, ferulic acid, (Z)-b-ocimene, and umbelliprenin.[87]

Ferula assafoetida extract

Respiratory system

The effect of *F. assafoetida* on H_1 receptors of TSM was

investigated using three concentrations of *F. assafoetida* extract and saline on the concentration-response curve to methacholine in incubated tissues with β-adrenergic and H_1 receptor antagonists (group 1) and β-adrenergic receptor antagonists alone (group 2). The results revealed that in the presence of atropine, *F. assafoetida* extract (at two higher concentrations), and saline, the methacholine EC_{50} values and maximum responses to methacholine varied. In both groups, the EC_{50} values were higher for atropine, as well as for the highest concentration of the extract (compared to saline). Furthermore, the CR-1 values were lower for the extracts compared to atropine in both groups. These findings suggest that the inhibitory effect of *F. assafoetida* on muscarinic receptors in TSM is influenced by H_1 receptor inhibition.[82,88] However, to fully understand the underlying mechanics and beneficial effects of these findings, more research is necessary.

Garcinia mangostana

Mangosteen, also known as *Garcinia mangostana* Linn., is a tropical evergreen tree native to southeast Asia and a member of the Clusiaceae family. It grows to a height of 6-25 meters and has dark-brown or practically black bark. The mangosteen tree produces a reddish/dark purple fruit with an edible, soft, juicy pulp and an appealing flavor. It is commonly referred to as "the queen of fruits". *G. mangostana* pericarp has been used in traditional medicine to treat a variety of diseases, including chronic ulcers, convulsions, fever, diarrhea, dysentery, infected wounds, pain, stomach discomfort, suppuration, and trauma. *G. mangostana* includes several kinds of components, such as anthocyanins, condensed tannins, flavonoids, phenolic acids, prenylated benzophenone derivatives, and xanthones (alpha- and gamma-mangostin).[89] Moreover, recent studies indicated antioxidant,[90] anti-inflammatory, antinociceptive,[91] antiapoptotic, cardioprotective,[92] and neuroprotective[93] properties of this fruit.

G. mangostana has also shown an inhibitory effect on H_1 receptors, which will be explained as follows:

Garcinia mangostana extract

Cardiovascular system

The contraction of the isolated rabbit aorta caused by histamine and serotonin was reduced by a crude methanolic extract of the fruit shell of *G. mangostana*. Using silica gel chromatography, the extract was fractionated while the pharmacological activity was being monitored to develop active components. The active components were determined to be alpha-mangostin and gamma-mangostin based on physicochemical data. In order to identify the pharmacological properties of alpha-mangostin the effect of the component on histamine H_1 and H_2 receptors was investigated by the observation of smooth muscle mechanical responses and measurement of radioligand binding to vascular smooth muscle cells in culture. The findings reveal that alpha-mangostin acts as a competitive selective antagonist of the histamine H_1 receptor.[83]

Garcinia mangostana main components

Cardiovascular system

In isolated rabbit thoracic aorta and guinea-pig TSM, alpha-mangostin inhibited histamine-induced contractions in a concentration-dependent manner. Alpha-mangostin caused a parallel shift in the concentration-contractile response curve to histamine. In the presence of chlorpheniramine, alpha-mangostin did not relax the rabbit aorta exposed to histamine. Further investigation demonstrated that alpha-mangostin induced a concentration-dependent inhibition of the binding of [^{3}H]mepyramine to rat aortic smooth muscle cells. Kinetic research showed that alpha-mangostin competitively reduced [^{3}H]mepyramine binding[84] (Table 2). The effect of alpha-mangostin on cultured vascular smooth muscle cells was shown that alpha-mangostin acted as a strong selective competitive histamine H_1 receptor antagonist.[83]

The effects of alpha-mangostin on histamine-induced contractions and receptor binding provide valuable insights into its pharmacological properties as a histamine H_1 receptor antagonist. The concentration-dependent inhibition of histamine-induced contractions by alpha-mangostin suggests its potential as an effective agent in modulating histamine-mediated responses. The parallel shift observed in the concentration-contractile response curve reinforce the competitive antagonistic effect of alpha-mangostin on H_1 receptors. However, further studies are needed to verify these findings in animal models and, eventually, in clinical trials. Also, more researches are needed to understand how alpha-mangostin inhibits H_1 receptors and competes with [^{3}H] mepyramine. Recognizing the molecular interactions and signaling mechanisms of alpha-mangostin can offer a deeper understanding of its pharmacological properties. Furthermore, the crude methanolic extract of *G. mangostana* fruit hull on isolated rabbit aortas shown to be effective in preventing histamine and serotonin-induced contractions. The ability of the extract to suppress histamine-mediated contractions may be due to the presence of compounds other than α-mangostin. More studies are needed to understand the different mechanisms of action of other components of the plant.

Ginkgo biloba

Ginkgo biloba, a unique living fossil from the Ginkgoaceae family, has shown notable morphological stability, with essentially no changes in form for over 200 million years. These trees may reach heights of 20-30 meters and have distinctively divided leaves, thus the species name "biloba". While *G. biloba* originated in China, Japan, and Korea, it is now grown all over the world for its nuts and leaves, both of which have therapeutic advantages. In traditional Chinese medicine, the nut-like gametophytes found in the seeds have been used to cure a variety of diseases, including coughs, asthma, enuresis, pyogenic skin disorders, and

intestinal tract worm infections. Additionally, these gametophytes have been used in traditional Chinese and Japanese cuisine.[94] Modern physiological research demonstrated the antioxidant,[95] anti-inflammatory,[96] anti-apoptotic,[97] immunomodulatory,[98] neuroprotective,[99] and cardioprotective[100] effects. The chemical composition of *G. biloba* includes a variety of compounds such as flavonoids, ginkgolic acids, lactones, polysaccharides, and terpene which are found in its exocarp, leaves, and seeds.[101]

In addition, the findings of investigations examined the effect of *G. biloba* on H_1 receptors will be discussed in the next paragraph.

Ginkgo biloba extracts

Nervous system

The effect of *G. biloba* extract on spatial memory deficits caused by diphenhydramine, pyrilamine, and scopolamine was investigated using rats' performance on an eight-arm radial maze in contrast to donepezil in order to elucidate the mechanism of *G. biloba* extract on learning and memory. The three metrics used to measure deficiencies in spatial memory were total error, reference memory error, and working memory error. Donepezil and *G. biloba* extract both had a strong antagonistic effect on the diphenhydramine-induced rise in total error, reference memory error, and working memory error. The spatial memory deficit caused by scopolamine was likewise counteracted by *G. biloba* extract and donepezil. While pyrilamine-induced spatial memory deficits showed a weak antagonistic effect of *G. biloba* extract, total error and working memory error showed a substantial difference. On the other hand, donepezil had no adverse effects on memory deficit induced by pyrilamine. These results led to the conclusion that cholinergic activity plays a major role in the effects of *G. biloba* extract, with a possible histaminergic mechanism contributing as well.[102]

The investigations on *G. biloba* extract provide information regarding its possible cognitive-enhancing properties as well as its interactions with the cholinergic and histaminergic systems. The observed decrease in memory deficit and amelioration of memory impairment emphasize the effectiveness of *G. biloba* in enhancing cognitive function. The ability to reduce memory impairment caused by pyrilamine and scopolamine indicates a protective effect against cholinergic and histaminergic disruptions. Furthermore, the H_1-antagonistic effect of crude extract demonstrated its potential in modulating histaminergic pathways. The findings suggest that the effect of *G biloba* extract on memory and cognitive function may be mediated, at least partially, through its interaction with the H_1 receptor. However, the specific mechanisms underlying the cognitive effects of *G. biloba* extract, as well as its interaction with cholinergic and histaminergic systems, require further investigation. Additionally, the bioavailability and appropriate dose of *G. biloba* extract for cognitive improvement must be investigated. More studies, including well-designed clinical trials, are needed to fully understand the advantages, mechanisms, and optimal uses of *G. biloba* extract for improving cognitive function and treating cognitive impairments.

Vascular system

In isolated porcine basilar arteries and endothelial disclosed cells, the extract of *G. biloba* leaf crude extract had no effect on extracellular $Ca^{2+}$and KCl induced contractions, however it exhibited H_1-antagonistic effect by preventing histamine-induced contraction which was eliminated in the presence of diphenhydramine[103] (Table 3).

Nigella sativa

Nigella sativa, a seed with a unique flavor, belongs to the Ranunculaceae family, also known as black seed or black cumin. It has a long history of usage as a natural remedy for numerous diseases in China, Syria, Turkey, Pakistan, and India, in addition to seasoning and food preservation. These include hepatotoxicity, neurotoxicity, renal toxicity, depression, rheumatoid arthritis, and cardiac damage. *N. sativa* contains several active compounds, including thymoquinone, dithymoquinone, thymohydroquinone, carvacrol, nigellicine, and nigellidine[50] The active components present in *N. sativa* seed and its oil exhibit a range of pharmacological effects, including anti-inflammatory, antioxidant,[111,112] immunoregulatory,[113,114] antihypertensive,[115] antitumor,[116] and antiasthmatic[114] properties. In the following part, the effect of *N. sativa* on H_1 receptors will be discussed.

Nigella sativa extracts

Respiratory system

An experiment was performed to investigate the inhibitory effect of aqueous and macerated *N. sativa* extracts on H_1 receptors in guinea pig TSM under different conditions. The extracts caused rightward shifts in histamine-response curves as compared to saline. The EC_{50} of histamine was reduced in the presence of extracts. These data indicate that *N. sativa* competitively inhibits histamine H_1 receptors.[104] The cumulative concentration response curves of $CaCl_2$-induced contractions of isolated guinea pig tracheal chains in the presence of calcium-free Krebs-Henseleit solution and KCl were measured in order to assess the calcium-antagonistic effects of three increment concentrations of the aqueous extracts of *N. sativa* and the calcium channel blocker diltiazem in comparison with saline. As compared to the saline control curves, a shift to the right was observed in the $CaCl_2$ response curves when two distinct concentrations of diltiazem and the aqueous extract were present. In the presence of two concentrations of aqueous extract and diltiazem, the effective concentration of $CaCl_2$ generating EC_{50} was substantially higher than saline. When the final concentrations of diltiazem and aqueous extract were

Table 3. The effects of *G. biloba*, *N. sativa*, *P. oleracea*, and their main components on histamine (H_1) receptors

Herb/Compound	Type of used cells, animals, and tissues	Doses	Results	Ref.
G. biloba EE	Male Wistar rats	20, 30, 50 mg/kg, p.o.	Antagonized spatial memory deficits Affected H_1 receptor	102
G. biloba leaf crude extract	*P*orcine basilar arteries and endothelial cells	25, 50, 100 µL/5 mL of organ bath fluid	Prevented histamine-induced contraction, eliminated by diphenhydramine	103
N. sativa AE, ME	Guinea pigs TSM	0.3, 0.05 mL	Rightward shifts in HRC ↑ EC_{50} histamine	104
N. sativa AE	Guinea pigs TSM	0.25, 0.5, 1 g%	H_1 blocking effects	105
N. sativa AE, ME	Guinea pigs TSM	0.25, 0.5, 1 g%	TSM relaxation H_1 blocking effects	106
Thymoquinone and *N. sativa* AE, ME	Guinea pigs TSM	TQ: 40, 80, 120 µM Extracts: 0.25, 0.5, 1 g% w/v	H_1 inhibitory effect No relaxant effect and H1 inhibitory effect of TQ	107
P. oleracea boiled and AEE	Guinea pigs TSM	0.25, 0.5, 0.75, 1.0, 1.25 w/v	H_1 blocking effects ↑TSM relaxation	108
P. oleracea AEE	Guinea pigs TSM	0.6, 0.12, 0.25 mg/mL	TSM relaxation H_1 receptors	109
P. oleracea AEE	Guinea pigs TSM	0.25, 0.50, 1.00 mg/mL	H_1 blocking effects Muscarinic Inhibitory effect	110

AEE: aqueous-ethanolic extract; AE: aqueous extract; EE: ethanolic extract; ME: methanolic extract; VSMC: vascular smooth muscle Cells; EC_{50}: 50% maximum response; Ref: reference; TSM: tracheal smooth muscle; HRC: histamine-response curves; TQ: thymoquinone.

present, the maximal response to $CaCl_2$ was less than that of saline. The highest concentrations of both diltiazem and aqueous extract did not result in the maximum response to $CaCl_2$, which may indicate that the aqueous extract has a functional antagonistic effect on calcium channels. The scientists came to the conclusion that this plant might interact with calcium channels because it has inhibitory effects on histamine (H_1) receptors and anticholinergic properties.[105]

In a different investigation, the probable effects of aqueous and macerated extracts of *N. sativa* on guinea pig tracheal chains were evaluated. In all three groups of tests, the inhibitory effects of both diltiazem concentrations were considerably larger than those of saline. In groups 1 (contracted by methacholine hydrochloride in the presence of ordinary Krebs solution) and 2 (contracted by methacholine hydrochloride in the presence of calcium free Krebs solution), the inhibitory effects of two higher concentrations of aqueous extracts were considerably higher than those of saline. Both higher macerated extract concentrations in group 1, all extract concentrations of this extract in group 2 had a substantially bigger impact than saline. In group 3 (contracted by KCl in the presence of ordinary Krebs solution), the extract did not exhibit any inhibitory effects. In groups 1 and 2, there was a strong relationship between the inhibitory effect and rising concentrations of diltiazem and extracts. Additionally, concentration response curves to methacholine and histamine in the presence of saline and plant extracts were used to demonstrate the anticholinergic and histamine H_1 receptor blocking effects of this plant on isolated guinea pig tracheal chains. The concentration response curves to histamine and methacholine shifted to the right in both investigations due to the plant extracts. The findings of this study indicate that *N. Sativa* may have bronchodilatory effects due to its anticholinergic, histamine H_1 inhibitory, and maybe potassium channel opening properties.[106]

To compare the relaxant effects of various thymoquinone concentrations to saline, theophylline, and *N. sativa* extracts on guinea pig TSM, two experimental groups were used: one with methacholine precontraction and another with KCl precontraction. Theophylline and *N. sativa* extracts showed significantly greater relaxant effects than saline in the methacholine-induced contraction group. However, in none of the studies did thymoquinone concentrations show a relaxant effect in either group. Theophylline and extracts showed much better relaxant effects than thymoquinone concentrations. In the KCl group, only theophylline had a substantial relaxant effect, whereas the extracts and thymoquinone had much lower effects than theophylline. These data indicate that the relaxant effect of *N. sativa* is not due to thymoquinone. The data suggest that histamine H_1 inhibitory may be responsible for the relaxant effect of the extract on TSM.[107]

N. sativa has demonstrated significant inhibitory effects on histamine H_1 receptors. Experiments show that both aqueous and macerated extracts of *N. sativa* cause rightward shifts in histamine-response curves, indicating competitive inhibition of H_1 receptors. The presence of *N. sativa* extracts reduces the EC_{50} of histamine, suggesting that the extracts inhibit the action of histamine. Additionally, the extracts exhibit relaxant effects on guinea pig TSM, which are not solely attributed to calcium channel blocking but may involve anticholinergic activity and potassium channel opening. While thymoquinone was tested, it showed lower relaxant effects compared to the extracts, indicating that the synergistic action of multiple components in *N. sativa* may be responsible for its overall effects. The findings indicate that multiple components in *N. sativa* may work synergistically to produce these effects, demanding further investigation into the specific active compounds responsible.

Portulaca oleracea

Purslane (*Portulaca oleracea* L.), belongs to the Portulacaceae Juss family, is widely distributed, and is native to tropical and subtropical regions. The name "Portulaca" is derived from the Latin words "porto," which means "to carry," and "lac," which translates as "milk," referring to the milky juice that this herb contains. Historically, *P. oleracea* has been used in traditional cuisine and folk medicine to treat a variety of ailments, including vermifuge, antiseptic, febrifuge, headaches, burns, arthritis, shortness of breath, as well as intestinal, stomach, and liver disorders. Its importance as a vital medicinal plant used by indigenous populations to cure a variety of ailments, including renal and cardiovascular illness, ulcers, diabetes, headaches, diarrhea, urinary infections, and bug and snake bites, has been further highlighted by ethnobotanical research,[117,118] The broad pharmacological potential of purslane and its components, including antioxidant,[119] anti-inflammatory, antimicrobial,[120] immunomodulatory,[121] and antidepressant,[122] properties, has been demonstrated by numerous studies. Bioactive compounds such as alkaloids, unsaturated fatty acids, flavonoids, minerals, polysaccharides, proteins, terpenoids, vitamins, and are abundant in *P. oleracea* and help maintain a healthy metabolic balance and prevent disease.[123]

Moreover, the effect of *P. oleracea* on H_1 receptors has been investigated in several studies, which will be discussed in the following section.

Portulaca oleracea extracts

Respiratory system

The relaxant effects of boiled and aqueous extracts of *P. oleracea* on guinea pig TSM were examined in three groups. In group 1, TSMs precontracted with KCl were tested using cumulative concentrations of the extracts and theophylline compared to saline. Significant relaxant effects were observed for higher concentrations of theophylline and boiled extract compared to saline. Theophylline had significantly greater relaxant effects than the boiled and aqueous extracts in this group. In group 2, TSMs precontracted with methacholine were tested without incubation. Both boiled and aqueous extracts and theophylline exhibited a concentration-dependent relaxant effect compared to saline. No significant differences were found when comparing the relaxant effects of the extracts with theophylline in this group. In group 3, TSMs precontracted with methacholine were incubated with propranolol plus chlorpheniramine to evaluate the contribution of H_1 histamine blocking effects. Both boiled and aqueous extracts and theophylline showed a concentration-dependent relaxant effect compared to saline. Most of the concentrations of both *P. oleracea* extracts that were obtained in the group 3 studies had relaxant effects that were not statistically different from those of group 2. These findings suggest probable histamine H_1 blocking properties of the plant extracts that may contribute to their relaxant effect on guinea pig TSM[108] (Table 3).

In another study, the effect of extract on isoprenaline concentration-response curves in TSM was assessed. Two groups were tested: non-incubated tissues and incubated tissues treated with chlorpheniramine. The results demonstrated that the concentration-response curves to isoprenaline in the presence of *P. oleracea* extract shifted to the left when compared to those obtained with saline in both groups. Considerably greater EC_{50} isoprenaline in the presence of propranolol than saline was observed in both groups. Furthermore, the EC_{50} values obtained with higher concentrations of the extract in group 1 and lower concentrations in group 2 were slightly lower than those obtained with saline, but the medium and high extract concentrations in group 2 significantly lowered the EC_{50} values. Moreover, the EC_{50} of isoprenaline in tissues incubated with chlorpheniramine (group 2) increased in comparison to non-incubated TSM (group 1). However, there was no significant difference in CR-1 values between the two groups. As a result, the findings from group 2 may indicate an inhibitory effect of the extract on histamine H_1 receptors.[109]

The effect of aqueous-ethanol extract of *P. oleracea* on muscarinic receptors in TSM was examined by performing concentration-response curves to methacholine in the presence of various concentrations of *P. oleracea* extract, atropine, and saline. Three experimental designs were employed: non-incubated tissues (group 1), incubated tissues with propranolol and chlorpheniramine (group 2), and incubated tissues with propranolol (group 3). The results showed that the concentration-response curves to methacholine were shifted to the right, and the EC_{50} values of methacholine were higher in the presence of atropine, the medium and highest extract concentrations in all groups, and the lowest extract concentration in group 3 when compared to saline. Furthermore, the EC_{50} value of methacholine at the high extract concentration in group 2 was greater than at the low and medium concentrations. All extract concentrations in all groups showed lower CR-1 values than atropine. These findings show that the *P. oleracea* extract has an inhibitory impact on muscarinic receptors in TSM and may block histamine H_1 receptors[110] (Figure 1).

In brief, the research conducted on guinea pig TSM demonstrated the relaxant properties of boiled and aqueous extracts of *P. oleracea*. Although the research provides valuable insights into the relaxant effects of *P. oleracea* extracts on TSM, there are certain limitations to consider. Future research should concentrate on elucidating the exact components of *P. oleracea* extracts and their interactions with relevant receptors in order to obtain a better understanding of the plant pharmacology. Despite these limitations, the advantage of these studies is that the findings are consistent across several studies, showing that *P. oleracea* showed a relaxant effect on TSM. Further study also should be conducted to assess the

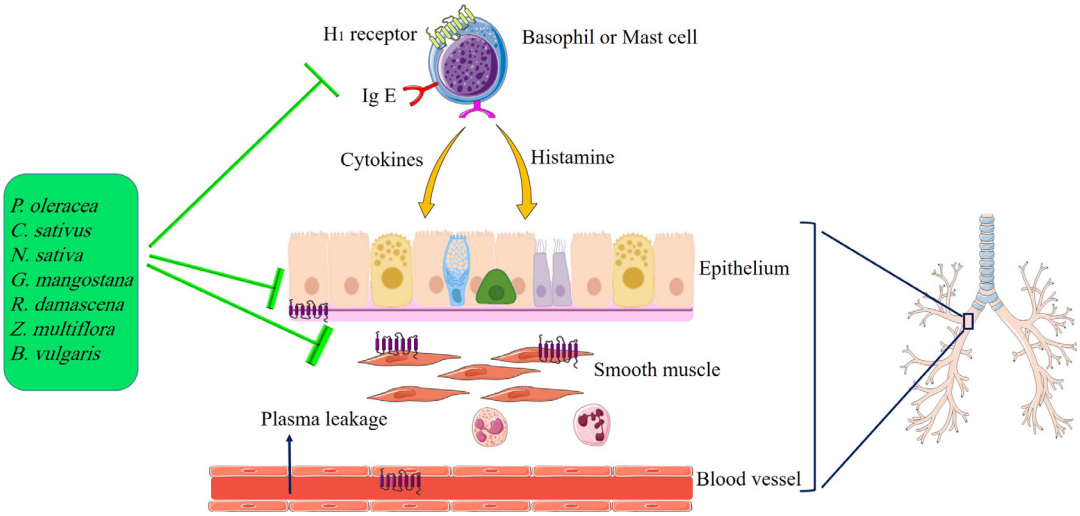

Figure 1. The proposed mechanism of bronchodilatory effects of some medicinal herbs by affecting Histamine H_1 receptors (Images from www.freepik.com and https://smart.servier.com)

effectiveness and safety of *P. oleracea* extracts in clinical trials in order to evaluate their suitability for human use.

Rosa damascena

Rosa damascena (Damask rose), is a tall shrub that grows to a height of 1 to 2 meters. It is recognized for its colorful and stunning flowers. This plant contains several components, including carboxylic acid, myrcene, terpenes, and vitamin C. It has been shown to have a variety of medicinal effects, as reported in ancient medical books, including the treatment of abdominal and chest pain, heart-strengthening properties, the management of menstrual bleeding, and digestive problems. It has also been identified for its anti-inflammatory and laxative effects and ability to relieve cough symptoms.[124] It has also been shown that *R. damascena* has bronchodilatory,[125,126] inotropic and chronotropic,[124] anticonvulsant,[127] and cardioprotective[128] properties. Some other investigations reported its inhibitory effects on H_1 receptors.

Rosa damascena extracts and essential oils

Respiratory system

The relaxant effects of the ethanolic extract and essential oils of *R. damascena* on guinea pig TSM were examined. In group 1, the effects of different concentrations of the extract, essential oils, and theophylline were compared to a saline control. Significant relaxant effects were observed at the highest concentrations of the extract, essential oils, and theophylline. In group 2, TSM that were not subjected to incubation and had been contracted using methacholine hydrochloride and higher concentrations of the extract, essential oils, and theophylline showed concentration-dependent relaxant effects compared to saline. The relaxant effects of essential oils were notably higher than those of theophylline and the extract. In group 3, that was incubated with chlorpheniramine, the extract and essential oil did not exhibit significant relaxant effects. This suggests a blocking effect on H_1 histamine receptors by the extract and essential oil of *R. damascena*[126] (Table 4).

The investigation on the relaxant effects of *R. damascena* on TSM provides useful information on its pharmacological properties. One strength of this study is the use of incubated tissues with propranolol and chlorpheniramine. This method enabled researchers to investigate the potential role of H_1 receptors in the relaxant properties of *R. damascena*. By comparing responses in non-incubated and incubated tissues, the researchers were able to identify an association between inhibitory activity of *R. damascena* and H_1 receptors. This finding contributes to our understanding of the mechanism of action of the plant, providing a base for future research and potential medicinal applications. However, the specific components of ethanolic extract and essential oil of *R. damascena* that cause the reported effects have not been discovered. Further studies on the effects of individual compounds of the plant might be useful in determining which components are largely responsible for the inhibitory effect on H_1 receptors. Additional research is required to determine the broader application and possible limits of these findings.

Silybum marianum

For almost 2000 years, *Silybum marianum* L., often known as milk thistle, has been used in folk medicine to treat a variety of diseases. It has earned a reputation as a medicinal herb that can treat liver, renal, and cardiac disorders, rheumatism, gastronomic disturbances, and gall bladder-related problems including jaundice, hepatitis, and cirrhosis. This tall, biennial plant may reach a height of 5 to 10 feet and is distinguished by its huge prickly leaves, massive purple blooming heads, and strong spine-fragrance stems. The term "milk thistle" comes from the milky veins on its leaves. *S. marianum* contains several components, including silymarin, flavonoids (apigenin, quercetin, and taxifolin), and flavonolignans (isosilybin, isosilychristin, silybin, silychristin, and silydianin).[135] Modern research reported multiple medicinal properties

for this plant, such as antioxidant,[136] anticancer,[137] anti-inflammatory,[138] hepatoprotective[139] and antidiabetic[140] effects.

Silybum marianum main components

Nervous system

The effect of silymarin on H_1 receptors was demonstrated by intraperitoneal administration to rats that received formalin. Silymarin reduced pain response in both phases of the test, but co-administration of chlorpheniramine and silymarin augmented the analgesic response.[129]

The study investigating the effect of silymarin on H_1 receptors provides valuable information about the possible analgesic properties of this compound. The research indicates that silymarin may have an extensive effect on pain modulation because it shows a decrease in pain response in both phases of the formalin test. Furthermore, the noted increase in the analgesic response with concurrent administration of silymarin and chlorpheniramine suggests a possible synergistic interaction between these substances. To confirm the analgesic advantages of silymarin in clinical trials, more research is required. Furthermore, additional studies are needed to determine the specific mechanisms resulting in the synergistic interaction with chlorpheniramine and the inhibitory effect on H_1 receptors.

Zataria multiflora

Zataria multiflora (Avishan-e-Shirazi or Shirazi thyme) is a perennial plant with a height range of 40 to 80 cm and tiny, woody leaves with a fibrous root system. It also has thin branches. This plant is only found in Afghanistan, Iran, and Pakistan. *Z. multiflora* contains a wide range of components, including bioactive substances, like terpenes such as thymol and carvacrol. It also includes 6-hydroxyluteolin glycosides, apigenin, di-, tri-, and tetramethoxylated substances, and luteolin. These components could be involved in the medicinal advantages of *Z. multiflora*. This herb is used in traditional medicine in Iran because of its antibacterial, analgesic, and carminative properties.[141] Additionally, it has been indicated that this plant has antioxidant,[142] immunomodulatory, anti-inflammatory,[143] antitumor,[144] and cardioprotective[145] properties. Furthermore, *Z. multiflora* has a relaxant effect on smooth muscles by affecting H_1 receptors, which will be explained in the following section.

Zataria multiflora extracts

Respiratory system

In two sets of guinea pig TSM, the effects of three different concentrations of *Z. multiflora* aqueous-ethanolic extract, chlorpheniramine, and saline were examined with a focus on H_1 receptors. In the first group, indomethacin was used to incubate the tissues, but in the second group, propranolol and indomethacin were used to do so. All of the extract concentrations in group 1 and the two higher concentrations of extract in group 2 had EC_{50} values that were significantly greater than those of saline in both groups when chlorpheniramine was present. The CR-1 values obtained in the presence of all three concentrations of the extract in group 1 and the highest concentration in group 2 were significantly higher than those of chlorpheniramine. The EC_{50} values for all three extract concentrations, as well as the CR-1 values for the two lower concentrations in group 2, were lower than those for group 1. There was no significant difference in the maximum response between the two groups when different extract concentrations were utilized. Concentration-response curves obtained with all concentrations of the extract in both groups showed a parallel rightward shift. These results indicate that *Z. multiflora* has an inhibitory effect on histamine H_1 receptors.[130,131] A further investigation, using three lower concentrations than the previous work, discovered that incubation of TSM with propranolol and chlorpheniramine caused parallel rightward shifts in methacholine-response curves. When the extract was present, maximum responses to methacholine increased significantly, as did the EC_{50}. These data show that the hydro-ethanolic extract may have inhibiting effects on H_1 receptors.[132] The relaxant effects of *Z. multiflora* aqueous-ethanolic extract on the guinea pig TSM were studied in one non-incubated TSM (group 1) and another with incubated tissues with chlorpheniramine (group 2). The findings of group 2, which comprised chlorpheniramine incubation, were comparable to group 1. The dose-response curves obtained in the presence of the extract in group 2 exhibited a lesser leftward shift than group 1. Furthermore, in the presence of the extract, EC_{50} values of group 1 were substantially lower than those in group 2. These data indicate that the extract has an inhibitory effect on H_1 histamine receptors.[133]

Two groups of TSM, one with no incubation and the other with propranolol and chlorpheniramine, were used to study the effects of three different concentrations of an aqueous-ethanolic extract of *Z. multiflora*, atropine, and saline on muscarinic receptors. In group 2, the tracheal preparation was incubated with propranolol and chlorpheniramine. The researchers assessed the inhibitory effects of the extract on these receptors as well as the role of β-adrenergic stimulatory and/or H_1 blocking effects on the functional antagonism of the extract on muscarinic receptors. Along with notable improvements in maximal responses to methacholine and a rise in EC_{50} in group 2 compared to group 1, the presence of extract caused a parallel rightward shift in the methacholine-response curves when compared to saline. These results point to possible competitive antagonistic effects of the hydro-ethanolic extract on muscarinic receptors. The findings from group 2 also suggest that the extract may have inhibitory effects on H_1 receptors as well as adrenergic stimulatory effects. Similar or possibly stronger antagonistic effects of the extract compared to atropine at the concentrations used are suggested by comparable or

even higher values of CR-1 observed in the presence of two lower concentrations of the extract and higher values of CR-1 in the presence of the highest concentration of the extract in group 2 relative to atropine. The maximum responses achieved with all concentrations of the extract remained considerably lower than those obtained with saline, even though the maximum responses of group 2 improved with the extract. These data show that the extract has mild functional antagonistic effects on muscarinic receptors, rather than β-adrenergic stimulatory and/or H_1 receptor inhibiting effects[134] (Table 4).

Another investigation evaluated the inhibitory effects of aqueous-ethanolic extract of *Z. multiflora* on H_1 receptors in guinea-pig TSM by performing histamine concentration-response curves in the presence of saline, the extract, and chlorpheniramine. The results revealed that EC_{50} histamine was substantially greater in the presence of chlorpheniramine than in saline. There were no significant variations in the maximal response among the groups at different extract concentrations. The concentration-response curves for the extract showed a similar rightward shift in all groups, demonstrating that *Z. multiflora* inhibited histamine H_1 receptors.[131]

Zataria multiflora main components

Respiratory system

The inhibitory effects of carvacrol on H_1 receptors in guinea pig TSM were investigated by conducting histamine concentration-response curves in the presence of saline, carvacrol, and chlorpheniramine. The results indicated that the histamine EC_{50} value was significantly higher in the presence of chlorpheniramine and carvacrol compared to saline. No significant differences were observed in the maximal response among the groups at different concentrations of carvacrol. The concentration-response curves for carvacrol exhibited a consistent rightward shift in all groups, indicating that carvacrol inhibited histamine H_1 receptors.[131]

According to the results of the studies on the plant and carvacrol, the aqueous-ethanolic extract of *Z. multiflora* and carvacrol relax smooth muscles by activating β2-adrenoceptors and suppressing H_1 receptors. The *Z. multiflora* extract also shows inhibitory effects on muscarinic receptors. These findings demonstrate the potential of *Z. multiflora* and carvacrol as bronchodilation therapy that targets several receptor pathways. One strength of these studies is the comprehensive exploration of the mechanisms underlying the bronchodilatory effects of *Z. multiflora* and carvacrol. This multi-target strategy allows for a more in-depth study of the pharmacological activities of *Z. multiflora* and carvacrol in bronchodilation. However, the experiments were mostly done on guinea pig TSM, which may not accurately reflect the complicated physiological conditions observed in human airways. Additional studies are required to verify these findings in human tissues and, eventually, in clinical trials. In addition, further research is needed to understand the molecular processes that inhibit H_1 and muscarinic receptors and stimulate β2-adrenoceptors and isolate individual compounds that are mainly responsible for the reported receptor interactions.

Conclusion

In this updated and comprehensive review, the effects of various medicinal plants and their constituents on histamine H_1 receptors have been explored, revealing their relaxant properties on smooth muscle, inhibitory effects on H_1 receptors, and potential cognitive-enhancing and analgesic effects. These findings underscore the significant potential of medicinal plants as a valuable resource for the development of innovative therapeutic interventions targeting conditions associated with histamine H_1 receptors.

Nevertheless, it is crucial to acknowledge the need for further research to validate these findings and gain a comprehensive understanding of the underlying mechanisms of action. While the studies discussed in this article provide intriguing evidence, more extensive investigations are necessary to identify the specific chemicals responsible for regulating H1 receptor activation and signaling pathways. Such identification would not only enhance our understanding of the pharmacological basis of medicinal plants but also facilitate targeted drug development.

Table 4. The effects of *R. damascena*, *S. marianum*, *Z. multiflora*, and their main components on histamine (H_1) receptors

Herb/Compound	Type of used animals and tissues	Doses	Results	Ref.
R. damascena EE, EO	Guinea pigs TSM	EEE: 0.25,-1.0 g% EO: 0.25-1.0 vol.%	TSM relaxation Histamine H_1 inhibitory effect	126
Silymarin	*In vivo*, Male Wistar rats	50, 100, 200, 400 mg/kg, i.p.	↑ Analgesic response due to chlorpheniramine + silymarin	129
Z. multiflora AEE	Guinea pigs TSM	2.5, 5, 10 µg/mL	TSM relaxation H_1 inhibitory effect	130
Z. multiflora AEE, carvacrol	Guinea pigs TSM	AEE: 2.5-10 µg/mL Carvacrol: 1, 2, 4 µg/mL	TSM relaxation H_1 inhibitory effect\	131
Z. multiflora AEE	Guinea pigs TSM	0.5, 1, 2 µg/mL	Histamine H1 inhibitory effect	132
Z. multiflora AEE	Guinea pigs TSM	0.5, 1.0, 2.0 µg/mL	TSM relaxation H_1 inhibitory effect	133
Z. multiflora AEE	Guinea pigs TSM	0.5, 1, 2 µg/mL	TSM relaxation H_1 inhibitory effect	134

AEE: aqueous-ethanolic extract; EE: ethanolic extract; EO: essential oil, Ref: reference; TSM: tracheal smooth muscle.

Furthermore, determining the appropriate doses and formulations of plant extracts or isolated chemicals is essential to ensure their efficacy and safety in clinical applications. Well-designed clinical trials are indispensable for assessing the safety, effectiveness, and long-term consequences of these therapies in human subjects.

Another promising avenue for exploration is the study of potential synergistic effects that can be achieved by combining multiple medicinal plants or their components. Investigating the combination therapies that integrate plant extracts with complementary mechanisms of action could yield valuable insights and potentially improve treatment outcomes while minimizing the risk of adverse effects.

In conclusion, this comprehensive review highlights the immense potential of medicinal plants in modulating histamine H_1 receptors and offers promising avenues for novel therapeutic interventions. However, further research is imperative to validate and expand upon the current findings, elucidate the underlying mechanisms, determine optimal dosing and formulations, and explore combination therapies. By advancing our knowledge in these areas, we can unlock the full therapeutic potential of medicinal plants in addressing conditions associated with histamine H_1 receptors.

Authors' Contribution

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Competing Interests

The authors declare that they have no conflicts of interest.

Consent to Participate

Not applicable.

Consent to Publish

Not applicable.

Data Availability Statement

No new data were created or analyzed during this study. Data sharing is not applicable to this article.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT and QuillBot in order to rephrase to reduce plagiarism, improve the language and grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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