Review Article
Use of Natural Products in Asthma Treatment

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Asthma, a disease classified as a chronic inflammatory disorder induced by airway inflammation, is triggered by a genetic predisposition or antigen sensitization. Drugs currently used as therapies present disadvantages such as high cost and side effects, which compromise the treatment compliance. Alternatively, traditional medicine has reported the use of natural products as alternative or complementary treatment. The aim of this review was to summarize the knowledge reported in the literature about the use of natural products for asthma treatment. The search strategy included scientific studies published between January 2006 and December 2017, using the keywords “asthma,” “treatment,” and “natural products.” The inclusion criteria were as follows: (i) studies that aimed at elucidating the antiasthmatic activity of natural-based compounds or extracts (in vitro and/or in vivo); and (ii) studies that suggested the use of natural products in asthma treatment by elucidation of its chemical composition. Studies that (i) did not report experimental data and (ii) manuscripts in languages other than English were excluded. Based on the findings from the literature search, aspects related to asthma physiopathology, epidemiology, and conventional treatment were discussed. Then, several studies reporting the effectiveness of natural products in the asthma treatment were presented, highlighting plants as the main source. Moreover, natural products from animals and microorganisms were also discussed and their high potential in the antiasthmatic therapy was emphasized. This review highlighted the importance of natural products as an alternative and/or complementary treatment source for asthma treatment, since they present reduced side effects and comparable effectiveness as the drugs currently used on treatment protocols.

1. Introduction

1.1. Physiopathology of Asthma. Asthma can be defined as a chronic inflammatory disorder that affects the lower airways, promoting an increase of bronchial reactivity, hypersensitivity, and a decrease in the airflow [1]. Furthermore, due to a complex interaction between the genetic predisposition and environmental factors, besides multiple related phenotypes, this disease may be considered as a heterogeneous disorder [2].

Sensitization by dust, pollen, and food represents the main environmental factors involved in the asthma physiopathology [1]. These antigens are recognized by the mast cells coated by IgE antibodies (Figure 1) and induce the release of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukins IL-2, IL-3, IL-4, IL-5, GM-CSF, prostaglandins, histamine, and leukotrienes [3, 4], by T lymphocytes and eosinophils. This degranulation process promotes an increase in the vascular permeability, leading to exudate and edema formation. This process is
followed by leukocyte migration to the tissue affected by the inflammatory process through chemotaxis mediated by selectins and integrins [3, 6]. Subsequently, the neutrophil migration to the inflammatory site and the release of leukotrienes LTB₄ induce the activation of type 2 cyclooxygenase (COX-2) and type 5 lipoxygenase (LOX-5), enhancing the expression of the C₃b opsonin that produces reactive oxygen species (ROS) and thus promoting cell oxidative stress and pulmonary tissue injury [3, 7].

Other mechanisms involved in asthma physiopathology are the inhalation of drugs, as well as respiratory viruses [8], which promote an immune response mediated by IgG antibodies. This process promotes an increase of the inflammatory cells influx, releasing inflammatory mediators responsible for the damage process [9].

Based on the factors and mechanisms presented above, asthma symptoms can be observed at different levels according to etiology and severity of clinical aspects, which define their classification [10]. The asthma severity is subdivided into (i) mild/low, also defined as intermittent/persistent, when the symptoms appear more than twice a week and their exacerbations can affect the daily activities of the patient; (ii) moderate, in which the daily symptom occurrence and their exacerbations affect the patient activities, requiring the use of short-acting β₂-adrenergic drugs; or (iii) severe asthma, in which the patient presents persistent symptoms, physical activity limitations, and frequent exacerbations [10]. Based on this classification, it is estimated that 60% of the asthma cases are intermittent or persistent, 25% to 30% are moderate, and the severe cases account for only 10% of the total. However, it is important to highlight that although the proportion of severe asthmatics represents the minority of the cases, they are responsible for high mortality and high hospitalization costs [11], evidencing the high need of efficient treatments for this disease.

1.2. Asthma Epidemiology. According to the World Health Organization, asthma affects about 300 million of individuals across the world, regardless of the country development degrees [12]. In the United Kingdom, asthma affects approximately 5.2 million of individuals and is responsible for 60,000 hospital admissions per year [13], while in Brazil the annual incidence of hospital admissions due to asthma is around 173,442 patients, representing 12% of the total admissions for respiratory diseases in 2012 [14].

Furthermore, studies have demonstrated that asthma incidence and prevalence rates in different countries are not age related. In the United States of America, Albania, and Indonesia, the asthma prevalence is lower for children (around 8.4%, 2.1%, and 4.1%, respectively) when compared to adults [15]. On the other hand, in countries such as the United Kingdom and Costa Rica, children aged between 6 and 7 years represent approximately 32% of the asthma prevalence [16]. Additionally, the incidence or prevalence can be directly influenced by the socioeconomic characteristics of specific areas, as demonstrated by the analyses of the annual variation in the prevalence of asthma in which it was possible to observe, in Spain, that the asthma prevalence had an annual increase of 0.44% regardless of the age range studied. However, when these same data analyses were
observed individually in Spain regions, the annual variation presented a different scenario, showing an increase or decrease according to the developmental degree of each region [17, 18]. Similar data were observed by Pearce et al. [19] and Schaneberg et al. [20], who demonstrated the influence of socioeconomic aspects on asthma. The studies showed a prevalent increase of asthma cases in metropolitan areas, fact attributed to the population growth with consequent exposure to the environmental factors and shortened access to asthma therapy, due to the high cost of the available medicines [19, 20]. Such phenomena directly interfere on the treatment compliance [21–23], evidencing the importance and the need of strategies that facilitate the access to the medicines for asthma therapy.

Studies that evaluate the importance of inclusion of antiasthmatic therapy on public health policy programs have demonstrated that asthma control can be achieved through a variety of approaches, promoting a decrease in hospital admissions of 90%. Indeed, this was demonstrated by two studies performed in Brazilian cities, in which public health programs offered free medicines and psychological and pharmaceutical care to treat chronic diseases [24, 25]. Furthermore, Ponte et al. [24] and Holanda [25] also showed that the hospital admissions of children decreased from 44.7% to 6.4% one year after the inclusion of these patients in the same project. Thus, these data corroborate the importance of public health policies that contribute to the reduction of hospital outlay, increasing the population’s life quality.

1.3. Asthma Treatment. The asthma treatment recommended by the Global Initiative for Asthma (GINA) consists, especially, on the reduction of symptoms in order to decrease the inflammatory process [26, 27]. However, since asthma presents a complex physiopathology associated with variable manifestations, the treatment can lead to different response levels. Thus, the evaluation of the clinical aspects associated with the treatment response is defined as the most adequate approach to achieve treatment success [28]. Asthma therapy strategies are based on pulmonary (the main administration route on asthma therapy), oral or intravenous administration of class β2 agonist drugs (salbutamol, levalbuterol, terbutaline, and epinephrine), anticholinergics (ipratropium), corticosteroids (beclomethasone di- or monopropionate, ciclesonide, flunisolide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, hydrocortisone, dexamethasone, budesonide, prednisone, prednisolone, and methylprednisolone), and xanthine drugs. Among these, the β2 agonists are often the drugs of first choice [13, 27].

To optimize the treatment for each patient, the drug dosage is determined by the patient’s respiratory characteristics, mainly his/her respiratory rate. Patients with increased respiratory rate, due to the airways narrowing, present a low dispersion of the inhaled drug through the respiratory tract [29]. In these cases or when there is an absence of response on the first two hours after treatment, hospitalization should be performed, and adrenaline could be used, subcutaneously or intravenously, since this is an indicative of mucosal edema formation, which can be decreased by the adrenaline bronchodilator effect [30].

Overall, patients that present asthma exacerbation should be initially treated with the association of different dosage of corticosteroids and short-acting β2 agonists by intranasal oxygen administration, allowing the stimulation of β2 receptors that result in bronchodilation due to the inhibition of cholinergic neurotransmission and, thus, inhibition of mast cells degranulation [10]. Additionally, corticosteroids by oral or inhaled route are used on uncontrolled persistent asthma patients due to their direct effect on the inflammation site [31]. Accordingly, they improve the pulmonary function and decrease the asthma episodes [32], reducing hospitalizations and mortality of asthmatic patients [31]. Furthermore, because their systemic use can induce side effects, corticosteroids, mainly prednisone and prednisolone, are more commonly used in patients with severe persistent asthma who are not stabilized by other drugs [31].

In addition, xanthine drugs such as theophylline can be also used on asthma treatment, since they are able to promote the suppression of monocyte activation with consequent inhibition on the TNF-α release. Further, they promote the inhibition of neutrophil activation and its degranulation, inhibiting the catalytic activity of phosphodiesterase 4 (PDE4), allowing a reduction in the inflammatory process [33].

Regardless of the wide variety and associations of antiasthmatic medicines and their ability to promote the asthma symptoms control and to reduce the asthma episodes and hospital admissions, the antiasthmatic drugs present several side effects, including nausea, headaches, and convulsions (xanthine class) [3, 30], cardiovascular effects (β-adrenergic receptors antagonists) [20], vomiting (PDE4 inhibitors drugs) [34–36], osteoporosis, myopathies, adrenal suppression, and metabolic disturb, compromising the patients’ growth (corticosteroids) [30, 35, 37, 38]. These side effects compromise the life quality of the patients and reduce significantly the treatment compliance.

Another important drawback from the conventional asthma treatment is its cost. In fact, the required amount of money for asthma treatments represents a significant expenditure for health public organizations. Such situation has become a financial issue even for developed countries. In Sweden, for example, the cost of medicines for asthma treatment has increased since the 1990s and, in 2006, it was responsible for 11.6% of the total healthcare expenditure. Furthermore, according to projections, an annual increase of 4% on the costs of asthma management is expected [22].

Additionally, studies revealed that in Europe and in the United States of America, the sum of the direct and indirect estimated annual costs with asthma management is approximately €18 billion and US$13 billion, respectively. This high expenditure was associated with the high incidence of uncontrolled asthma patients, since they represent an expense up to 5-fold higher than the controlled asthma ones [39] or than patients with other chronic diseases, as
demonstrated in the study performed by O’Neil and colleagues [40]. These authors revealed that asthma costs up to £4,217 per person, while type II diabetes, chronic obstructive pulmonary disease, and chronic kidney disease represented, together, a cost of £3,630 [40].

Therefore, considering the therapies currently available, their side effects, and their high cost, the development of new therapeutic approaches or complementary treatments to the current asthma therapy become an important and essential strategy. In this context, the use of natural products allows easy access to treatment to all socioeconomic classes [41, 42] and shows advantages such as low cost, biocompatibility, and reduced side effects, besides their wide biodiversity and renewability [43, 44]. In addition, natural products, supported by the literature findings on their complex matrix as a source of bioactive compounds, represent one of the main access forms to the basic healthcare in the traditional medicine [45]. Thus, the present review aimed at summarizing the main natural products reported in the literature that show antiasthma activity.

2. Natural Products as Alternative for Asthma Treatment

The use of natural products for the treatment of physiologic disorders, especially in association with other drugs, has been widely reported through ethnopharmacological studies as an important scientific tool for bioprospection exploration and discovery of new bioactive compounds from natural sources [46]. Despite the wide scientific progress regarding chemical and pharmaceutical technology on synthesizing new molecules, drugs from natural sources still contribute tremendously to the discovery and development of new medicines [47]. These studies are based, initially, on the traditional use of the natural products, which draws the attention of pharmaceutical companies due to their easy and economical use, allowing the companies to perform many studies that evaluate their therapeutic activities, their toxicity, and their safety [48].

Moreover, the use of natural products as complementary therapy represents an important alternative for the treatment of several diseases [49]. In the United States of America, the use of natural products, vitamins, and other dietary supplements as auxiliary treatments represent about 40% of the conventional therapies [50]. Among the diseases that natural products are used for, those of allergic and inflammatory character can be highlighted. In fact, according to the literature, the alternative medicine associates the use of these products with biochemical mechanisms involved in immunomodulation, which could contribute to the management of these diseases [51].

The use of plant-based products for asthma treatment has been reported by the traditional medicine for over 5000 years, since the use by the Chinese culture of the infusion of Ephedra sinica, which is as an immune system stimulator able to decrease asthma crises [20]. More recently, a study performed by Costa and colleagues [49] described the main natural sources for the treatment of asthma used by the Brazilian families from the Northeast Region of the country [49]. The study included beet, honey, onion, lemon, garlic, yarrow, and mint, demonstrating the wide variety of natural products used on asthma treatment in children [49]. Additionally, other natural-derived products have been widely cited in asthma treatment, such as natural oils from plants and animals, which can be obtained by different extraction process [52, 53].

Plant-derived natural oils represent the main natural products used on the complementary asthma therapy due to the presence of compounds such as phenylpropanoids and mono- and sesquiterpenes as the major bioactive compounds, which provide their anti-inflammatory, antifungal, antibacterial, and anesthetic properties [54–56]. Similarly, oils obtained from animal sources have been used. They are rich in a mixture of different saturated, mono and polyunsaturated fatty acids, as well as compounds from animal organs and secretions, which are responsible for the immune-modulatory action and regulation of the tissue oxidative capacity [57, 58]. The activity credited to the oils derived from plants and animals is related to the presence of those bioactive compounds, which can inhibit COX-2 and COX-5. Additionally, these compounds are able to modulate the immune cells function by reducing levels of IL-4, IL-5, and IL-13 cytokines, decreasing the activity and proliferation of NK cells and leading to an increase in the level of endogenous corticosteroids, contributing to the regulation of NF-κB pathway, and reducing the mucus production and the inflammation in the lung tissues [59–61].

In this regard, Table 1 shows all products found in the studies included in this review after the inclusion criteria evaluation. Due to the wide variety of plant-derived products, only those with 3 or more citations were described in detail in this review. On the other hand, due to limited scientific investigations about the antiasthmatic activity of the natural products from animal and microorganism sources, all studies that fit the inclusion criteria were described in the next sections.

2.1. Natural Products from Plants. The use of natural products obtained from plants by the traditional medicine has been reported from centuries, especially in countries as China, Japan, and India [212]. Thus, the topics below concern these products or bioactive compounds originated from the most studied plants used on asthma therapy.

2.1.1. Flavonoids. Flavonoids are natural compounds from plants, nuts, and fruits that are chemically characterized by the presence of two benzene rings (A and B) linked through a heterocyclic pyrene ring (C). They represent a large group of polyphenolic secondary metabolites [213] with more than 8,000 different compounds already identified [214]. Considering their chemical structure, they can be classified as flavans, flavonones, isoflavonones, flavones, isoflavones, anthocyanidins, and flavonolignans [214]. Flavans or isoflavans possess a heterocyclic hydrocarbon skeleton, chromane, and a substitution on its C ring, in carbons 2 or 3, by a phenyl group (B ring). Flavanones and isoflavanones show an oxo-group in position 4. The presence of a double bond
| Product | Product form | Product source | Active compound | Compound class/type | Mechanism of action | Reference |
|---------|--------------|----------------|-----------------|---------------------|---------------------|-----------|
| 1,8-Cineol | Isolated compound | Essential oil of *Eucalyptus globulus* leaves | 1,8-Cineol | Monoterpene | Reduces the expression of NF-κB target gene MUC2 | Greiner et al. [62] |
| 3-Methoxy-catalposide | Isolated compound | *P. rotundum* var. *subintegrum* extract | 3-Methoxy-catalposide | Iridoid glycoside | Inhibits the expression of cylooxygenase (COX)-2, nitric oxide synthase (iNOS), and proinflammatory genes (IL-6, IL-1β, and TNF-α) | Ryu et al. [63] |
| *Achyranthes aspera* L. | Ethanolic extract | Roots | Not reported | Not reported | Bronchoprotective activity | Dey [64] |
| *Ailanthus excelsa* Roxb | Aqueous extract | Barks | Not reported | Not reported | Bronchodilator and mast cell stabilizing activities | Kumar [65] |
| *Allium Cepa* L. and quercetin | Extract and isolated compound | Methanolic extract and vegetable | Quercetin [2-(3, 4-dihydroxyphenyl)-3, 5, 7-trihydroxy-4H-1-benzopyran-4-one, 3, 3′, 4′, 5, 6-entahydroxyflavone] | Flavonoid | Reduce the production of proinflammatory cytokines (IL-4, IL-5, IL-13) and promote the relaxation of tracheal rings | Oliveira et al. [66] |
| *Alstonia scholaris* (L.) R. Br. | Extract | Leaves of *Alstonia scholaris* (L.) R. Br. | Scholaricine, 19-epi-scholaricine, vallesamine, picrinine | Alkaloid | Reduce the eosinophilia, the production of proinflammatory cytokine (IL-4) and the expression of serum IgE and eotaxin | Zhao et al. [67] |
| *Amorphophallus konjac* (konjac) | Gel extract | Not reported | Not reported | Plant | Not elucidated | Chua et al. [68] |
| *Andropogon maricatus* | Crude extract | Aerial parts | Vetivenes, vetivenol, vetivenic acid, and vetivenyl acetate | Sesquiterpenic compounds | Inhibit the Ca\(^{2+}\) channels and phosphodiesterase activity | Shah and Gilani [69] |
| *Anoectochilus formosanus* Hayata | Aqueous extract | Whole plant | Kinsenoside | Plant | Reduce the IL-4 production by Tregs and enhance the production of IL-12 and IFN-γ by Th1 differentiation | Hsieh et al. [70] |
| *Artemisia maritima* | Essential oil | Leaves | 1,8-Cineol, camphor, camphene, and β-caryophyllene | Terpenoid | Inhibit the Ca\(^{2+}\) channels and phosphodiesterase activity | Shah et al. [71] |
| *Aster tataricus* L. f. | Extract | Rhizomes | Kaempferol, aurantiamide, and astin C | Flavonoid | Inhibit the expression of NF-κB and promote the activation of beta-2 adrenergic receptor | Chen and Zheng [72] |
| Product                                    | Product form          | Product source         | Active compound                                | Compound class/type                  | Mechanism of action                                                                 | Reference                  |
|-------------------------------------------|-----------------------|------------------------|------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|
| *Aster yomena* (Kitam.) Honda              | Ethanolic extract     | Leaves                 | Phenolic compounds not specified                | Phenolic compounds                   | Attenuate the production of NO and IL-1β, and suppress the expression of NF-κB. In addition, suppress the activation of TLR4 and promote a reduction of intracellular ROS production | Kang et al. [73]            |
| *Baicalin*                                | Isolated compound     | Leaves and branch      | 7-Glucuronic acid-5,6-dihydroxyflavone           | Flavonoid                            | Suppress the lipopolysaccharide-induced TNF-α expression and inhibit the cyclic adenosine monophosphate-specific phosphodiesterase 4 (PDE4) | Park et al. [74]             |
| *Baliospermum montanum Miihl Arg.* (Euphorbiaceae) | Chloroformic and ethanolic extracts | Leaves                 | Alkaloids, triterpenoids, diterpenoids, and glycosides | Alkaloids, triterpenoids, diterpenoids, and glycosides | Stabilize the mast cell degranulation and decrease the histamine release                  | Venkatesh et al. [75]      |
| *Berry fruit*                             | Polyphenolic extract  | Not reported            | Phenolic compounds not specified                | Phenolic compounds not specified     | Not reported                                                                         | Power et al. [76]           |
| *Boswellia serrata, Boswellia carterii, and frankincense* | Essential oil         | Resinous part           | Fl-boswellic acid, acetyl-fl-boswellic acid, and 11-keto-fl-boswellic acid, and acetyl 11-keto-fl-boswellic acid | Boswellic acids                      | Inhibition of leukotriene biosynthesis                                                | Hamidpour et al. [77] and Al-Yasiry and Kiczorowska [78] |
| *Boswellia serrata, Glycyrrhiza glabra, and Curcuma longa* | Essential oil extract and extract | Resinous part, licorice root and turmeric root, respectively | Curcumin and fl-boswellic acid | Polyphenol | Reduce the plasma level of the leukotriene C4, nitric oxide and malondialdehyde | Houssen et al. [79]         |
| *Buffalo spleen lipid and a bacterial polypeptide* | Extract               | Animal-derived and microorganism-derived, respectively | Not reported | Not reported | Reduce the tracheal responsiveness and the amount of white blood cells               | Neamati et al. [80]         |
| Bullfrog oil (*Rana catesbiana shaw*)     | Oil                   | Bullfrog adipose tissue | Oleic, linolenic, stearic, palmitic, and myristic acids. Eicosapentaenoic acids and docosahexaenoic acid | Fatty acids | Not elucidated                                                                     | Amaral-Machado et al. [81] |

Table 1: Continued.
| Product | Product form | Product source | Active compound | Compound class/type | Mechanism of action | Reference |
|---------|--------------|----------------|----------------|--------------------|--------------------|-----------|
| **Bu-zhong-yi-qi-tang** | Aqueous extract | Root of Astragalus mongholicus Bunge, Panax ginseng C.A.Mey, Angelica dah-rica Fisch. Ex Hoffm and Bupleurum chinense DC. Rhizome of Zingiber officinale Rosc, Atractylodes macrocephala Koidz, and Cimicifuga foetida L. Fruit of Ziziphus jujuba Mill. var. inermis Rehd. Pericarp of Citrus reticulata Blanco. Root and rhizome of Glycyrrhiza uralensis Fisch | Not reported | Not reported | Reduce the level of eotaxin, Th2-related cytokines (IL-4, IL-5, IL-13), IgE, and eosinophilia | Yang et al. [82] |
| **Caenorhabditis elegans** | Crude extract | Microorganism | Not reported | Not reported | Modulate the immunologic Th1/Th2 response | Huang et al. [83] |
| **Camellia sinensis** L. | Aqueous extract | Not reported | Polyphenols and flavonoids | Polyphenols and flavonoids | Not elucidated | Sharangi [84] |
| **Carica papaya** | Extract | Leaves | Tanins, alkaloids, steroids, and quinones | Tanins, alkaloids, steroids, and quinones | Reduce the expression of IL-4, IL-5, eotaxin, TNF-α, NF-κB, and iNOS | Elgadir et al. [85] |
| **Carum roxburghianum** | Crude extract | Seeds | Hydrocarbons, wax esters, sterol esters, triacylglycerols, free fatty acids, diacylglycerols, lysophosphatidylethanolamines, and phosphatidylinositol | Hydrocarbons, wax esters, sterol esters, triacylglycerols, free fatty acids, diacylglycerols, lysophosphatidylethanolamines, and phosphatidylinositol | Bronchodilator activity | Khan et al. [86] |
| Chitin | Isolated compound | Shrimp | Chitin | Polysaccharide | Not elucidated | Ozdemir et al. [87] |
| Chrysin | Isolated compound | Marketable synthetic compound | 5,7-Dihydroxy-2-phenyl-1-4H-chromen-4-one | Flavonoid | Reduces the histamine release and decreases the gene expression of proinflammatory cytokines (IL-1β, IL-4, IL-6, TNF-α, NF-κB) | Yao et al. [88]; Yao et al. [89]; Bae et al. [90] |
Table 1: Continued.

| Product                                      | Product form | Product source         | Active compound                        | Compound class/type | Mechanism of action                                                                 | Reference                     |
|----------------------------------------------|--------------|------------------------|----------------------------------------|---------------------|-------------------------------------------------------------------------------------|-------------------------------|
| **Cissampelos sympodialis Eichl**           | Extract      | Leaves                 | Warifteine                             | Alkaloid            | Reduce the expression of IL-3 and IL-5, increase the IL-10 level, and decrease the density of inflammatory cells | Cerqueira-lima et al. [91]    |
| **Citrus tachibana**                         | Ethanol extract | Leaves              | Coumarins, carotenoids, and flavonoids | Coumarins, carotenoids, and flavonoids | Modulate the Th1/Th2 imbalance by inhibition of NF-κB signaling and histamine secretion | Bui et al. [92]               |
| **Conjugated linoleic acid**                 | Conjugated compound Fatty tissue from ruminants | Cis, cis-9,12-octadecadienoic acid | Polyunsaturated fatty acid             |                    | Modulate the PPAR-dependent and PPAR-independent inflammation signaling, the eicosanoid production, and humoral immune response | Macredmond and Dorscheid [93] |
| **Coumarins**                                | Isolated compound Synthetic compounds | 6,7-Dihydroxycoumarin, 7-hydroxycoumarin and 4-methyl-7-hydroxycoumarin | Coumarin               | Not elucidated                  |                                                                          | Sanchez-Recillas et al. [94] |
| **Croceltin**                                | Isolated compound Marketable synthetic compound | Crocetin                     | Carotenoid                             |                     | Activates the FOXP3 signaling through TIPE2                                      | Ding et al. [95]             |
| **Curcumin**                                 | Isolated compound Curcuma longa | (1E, 6E)-1,7-Bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione | Polyphenol                                    |                     | Inhibits the Notch1-GATA3 signaling pathway                                       | Zheng et al. [96]; Chong et al. [97] |
| **Cyclotheonamides**                         | Isolated compound Marine | Not reported            | Cyclic pentapeptides                   |                    | Inhibit the human β-tryptase                                                     | Schaschke and Sommerhoff [98] |
| **Diallyl-disulfide**                         | Isolated compound Garlic oil | Diallyl-disulfide       | Organosulfur                           |                     | Activates the Nrf2/HO-1 pathway and suppresses the NF-κB                           | Shin et al. [99]             |
| **Dietary plant stanol esters**              | Not reported  | Fatty acid              | Not reported                           | Stanol ester        | Reduce the total plasma IgE, IL-1β, IL-13, and TNF-α                              | Brull et al. [100]           |
| **Dioscorea nipponica**                      | Isolated compound Not reported | Diosgenin              | Steroidal saponin                      |                     | Suppress the secretion of TNF-α, IL-1β, and IL-6                                  | Junchao et al. [101]          |
| **D-α-tocopheryl acetate**                   | Isolated compound Natural source | D-α-tocopheryl acetate | Vitamin                               |                     | Inhibits the oxidative stress, Modulates the allergic inflammation and the airway hyperresponsiveness | Hoskins et al. [102]         |
| Product | Product form | Product source | Active compound | Compound class/type | Mechanism of action | Reference |
|---------|--------------|----------------|-----------------|---------------------|---------------------|-----------|
| *Echinodorus scaber* | Hydroethanolic extract | Leaves | Vitexin, rutin, and gallic acid | Phenolic compounds | Decrease the migration of inflammatory cells and reduce the Th2 cytokines and IgE levels | Rosa et al. [103] |
| *Eclipta prostrata (L.) L.* | Methanolic extract | Whole plant | Wedelolactone and demethylwedelolactone | Coumestan | Reduce the bronchial hyperresponsiveness and the production of Th2 cytokines | De Freitas Morel et al. [104] |
| *Ecklonia cava* | Marine alga | Brown macroalgae | Fucodiphloroethol and phlorofucofuroeckol A | Phlorotannins | Downregulate the FcεRI expression and block the IgE-FcεRI binding | Vo et al. [105] |
| *Ephedra intermedia* | Crude extract | Aerial parts | Ephedrine and pseudoephedrine | Alkaloids | Not elucidated | Gul et al. [106] |
| Ellagic acid | Isolated compound | Marketable synthetic compound | Ellagic acid | Polyphenol | Inhibits the activation of the NF-κB | Zhou et al. [107] |
| Emodin | Isolated compound | Roots and barks of *Rheum palmatum* and *Polygonum multiflorum* | 1,3,8-Trihydroxy-6-methylandrubquinone | Anthraquinone | Suppresses the characteristics of airway inflammation, mucin components, and chitinase protein expression. Inhibits the NF-κB signaling pathway | Shrimali et al. [108] |
| *Euphorbia hirta* | Aqueous extract | Not reported | Galloylquinic acid, phorbol acid, leucomycinidol, quercitol, camphol, quercetin, chlorophenolic acid, shikimic acid | Tanins, leucoanthocyanidins, flavonoids, and phenolic compounds | Not elucidated | Kunwar et al. [109] |
| Sesame | Fixed oil | Seeds | 5,5′-(1S, 3aR, 4S, 6aR)-Tetrahydro-1H, 3H-furo[3,4-c]furan-1,4-diybis-1,3-benzodioxole | Polyphenol | Decreases the levels of IL-4, IL-5, IL-13, and serum IgE. Reduces the amount of inflammatory cells and the eosinophil infiltration | Lin et al. [41] |
| Farnesol | Isolated compound | Fruits, leaves, flowers | 3,7,11-Trimethyl-2,6,10-dodecatrienal-1-ol | Sesquiterpene | Increases the level of IgG2a/IgE and reduces the total IgE, IgA, IgM, IgG | Ku and Lin [110] |
| Feverfew (*Tanacetum parthenium* L.) | Extract | Leaves and parts above the ground | Parthenolide | Sesquiterpene | Inhibit the IκB kinase complex and the histamine release | Pareek et al. [111] |
**Table 1: Continued.**

| Product                  | Product form     | Product source                                                                 | Active compound                          | Compound class/type | Mechanism of action                                                                                                           | Reference                      |
|--------------------------|------------------|-------------------------------------------------------------------------------|------------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Flavonoids               | Isolated compound| Vegetables (capers, tomatoes, fennel, sweet potato leaves, etc.), fruits (apple, apricots, grapes, plums, and berries), cereals (green/ yellow beans and buckwheat) | Not reported                                   | Polyphenol           | Prevent the IgE synthesis and the mast cell degranulation. Reduce the airway hyperresponsiveness and inhibit the human phospholipase A2 | Castell et al. [112]; Lattig et al. [113] |
| *Fumaria parviflora* Linn | Aqueous methanolic extract | Aerial parts                                                                   | Fumarophycine, cryptopine, sanactine, stylopine, bicuculline, adlumine, perfumidine, and dihydrosanguirinine | Alkaloids            | Block the muscarinic receptors and the Ca<sup>2+</sup> channels                                                            | Najeeb ur et al. [114]         |
| Galangin                 | Synthetic compound | *Alpinia officinarum*                                                         | 3,5,7-Trihydroxy-2-phenylchromen-4-one    | Flavonol            | Inhibits the TGF-β1 signaling by ROS generation and MAPK/ Akt phosphorylation                                               | Liu et al. [115]               |
| *Geastrum saccatum*      | Solid extract     | Fruiting bodies of *Geastrum saccatum*                                         | β-Glucose                                 | Polysaccharide       | Inhibit the NOS and COX                                                                                                    | Guerra dore et al. [116]       |
| Ginsenosides             | Synthetic compound | Root of ginseng                                                                | Ginsenosides                              | Glycoside           | Suppress the IL-4 level, increase the production of IFN-γ, and inhibit the mucus overproduction and recruitment of eosinophils | Chen et al. [117]              |
| Grape seed               | Extract           | Seeds                                                                          | Not reported                              | Not reported        | Not elucidated.                                                                                                             | Mahmoud [118]                  |
| *Gymnema sylvestre* R. Br. | Extract         | Leaves                                                                         | Not reported                              | Tanins and saponins | Not elucidated.                                                                                                             | Tiwari et al. [119]; Di Fabio et al. [120] |
| *Herba epimedi*          | Extract           | Leaves                                                                         | Icariin                                   | Flavonoids, iridoid glycosides, and alkaloids | Inhibit the mRNA expression of TGF-β1 and TGF-β2. Modulate the TGF-β signaling                                              | Tang et al. [121]              |
| Higenamine               | Isolated compound | *Tinospora crispa*, *Nandina domestica Thunberg*, *Gnetum parvifolium* C.Y. Cheng, *Asarum heterotropoides* | 1-[(4-Hydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol | Alkaloid            | Not elucidated                                                                                                             | Zhang et al. [122]             |
| Homoeogonol              | Isolated compound | *Styrax japonica*                                                              | 3-[2-(3,4-Dimethoxyphenyl)-7-methoxy-1-benzofuran-5-yl] propan-1-ol | Lignan              | Reduces the inflammatory cells count and Th2 cytokines                                                                   | Shin et al. [123]              |
| Product          | Product form | Product source     | Active compound         | Compound class/type                      | Mechanism of action                                                                 | Reference  |
|------------------|--------------|--------------------|-------------------------|------------------------------------------|-------------------------------------------------------------------------------------|------------|
| Hypericum sampsonii | Isolated compound | Aerial parts | Not reported | Polycyclic polyprenylated acylphloroglucinols | Not elucidated                                                                      | Zhang et al. [124] |
| Justicia pectoralis  | Extract        | Aerial parts | 7-Hydroxycoumarin      | Coumarin                                 | Decrease the tracheal hyperresponsiveness and the IL-1β and TNF-α levels             | Moura et al. [125] |
| Juniperus excelsa    | Crude extract  | Aerial parts | (+)-Cedrol, (+)-Sabinene, (+)-limonene, terpinolene, endo-fenchol, cis-pinene hydrate, α-campholen, camphor, borneol, triene cycloheptane 1,3,5-trimethylene, β-myrcene, α-allyl toluene | Anthraquinones, flavonoids, saponins, sterol, terpenoids, and tanins | Inhibit the Ca^{2+} influx and the phosphodiesterase activity                         | Khan et al. [126] |
| Kaempferol          | Isolated compound | Biotransformation of synthetic kaempferol by genetically engineered E. coli | Kaempferol-3-O-rhamnoside | Flavonoid                                 | Reduces the inflammatory cells number, suppresses the production of Th2 cytokines and TNF-α | Chung et al. [127] |
| Kefir              | Isolated compound | Kefir grains       | Kefiran                 | Microorganism derived                    | Reduces the inflammatory cell number and decreases the level of IL-4, IL-13, IL-5, and IgE | Kwon et al. [128]; Lee et al. [129] |
| Laurus nobilis L.   | Isolated compound | Leaves of Laurus nobilis L | Magnoliolide           | Sesquiterpene                           | Inhibit the mast cell degranulation and reduce the IL-4 and IL-5 production          | Lee et al. [130] |
| Lepidium sativum    | Crude extract  | Seeds              | Ascorbic acid, linoleic acid, oleic acid, palmitic acid, stearic acid | Vitamin and fatty acids                  | Promote an anticholinergic effect, inhibit the Ca^{2+} influx, and inhibit the phosphodiesterase activity | Rehman et al. [131] |
| L-Theanine          | Isolated compound | Green tea of Camellia sinensis | L-Theanine (N-ethyl-L-glutamine) | Amino acid                              | Reduces the ROS production and decreases the levels of NF-κB and MMP-9               | Hwang et al. [132] |
| Luteolin            | Isolated compound | Perilla frutescens | (2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromenone) | Flavonoid                               | Inhibits the mucus overproduction and the GABAergic system                          | Shen et al. [133] |
| Product                          | Product form | Product source | Active compound                                                                 | Compound class/type | Mechanism of action                                                                 | Reference       |
|---------------------------------|--------------|----------------|---------------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------|-----------------|
| Lysate bacterial (OM-85 Broncho-Vaxom) | Extract      | H. influenzae, S. pneumoniae, Klebsiella pneumoniae, smelly nose Klebsiella, S aureus, Streptococcus pyogenes, Streptococcus viridans, Neisseria catarrhalis | Not reported        | Not reported                                                                    | Increase the level of IL-4, IL-10, and IFN-γ | Lu et al. [134] |
| Mangifera indica L. extract (Vimang®) | Extract      | Stem bark       | Mangiferin (1,3,6,7-tetrahydroxycoumarin-c2-b-D-glucoside)                        | Xanthone            | Inhibit the IgE production, the histamine release, and mast cell degranulation. Decrease the MMP-9 activity Reduce the inflammatory cells recruitment and the airway hyperresponsiveness. Increase the Th2 cytokines and attenuated the increase of the PIK3 activity | Rivera et al. [135] |
| Aqueous extract                 | Barks        | Mangiferin (1,3,6,7-tetrahydroxycoumarin-c2-b-D-glucoside)                        | Xanthone            |                                                                                  |                                                                    | Alvarez et al. [136] |
| Mangosteen                      | Isolated compound | Garcinia mangostana Linn. | α- and γ-mangostin                                                               | Xanthone            | Inhibits the histamine release and modulates the cytokine production               | Jang et al. [137] |
| Marine bioactives               | Isolated compound | Marine sponges Petrosia contignata and Xestospongia bergquista | Contignasterol and xestobergsterol                                               | Steroids            | Upregulation of TNF-β and IL-10 expression                                           | D’Orazio et al. [138] |
| Marshallagia marshalli          | Isolated compound | Marshallagia marshalli | Secretory/excretory antigen                                                       | Microorganism derived | Prevent the release of TNF-α and IL-1β. Suppress the neutrophil migration         | Jabbari et al. [139] |
| Mikania laevigata and M. glomerata | Extract      | Leaves          | Dihydrocoumarin, coumarin, spathulenol, hexadecanoic acid, 9, 12-octadecadienoic acid, 9, 12,15-octadecatetraenoic acid, cupressenic acid, kauremol, kaurenoic acid, isopropylxigandilfloric acid, isobutyloxy-grandifloric acid | Coumarins, terpenoids, steroids, and flavonoids | Not elucidated                                                                  | Napimoga and Yatsuda [140] |
Table 1: Continued.

| Product                      | Product form          | Product source  | Active compound                     | Compound class/type | Mechanism of action                                                                 | Reference         |
|------------------------------|-----------------------|-----------------|-------------------------------------|---------------------|-------------------------------------------------------------------------------------|-------------------|
| Milk and colostrum           | Conjugated compound   | Bovine milk    | Conjugated linoleic acid            | Fatty acid          | Modulate the cytokine and antibodies (IgE, IgM) production, interferon NO synthesis and iNOS activity. Modulate the mast cell degranulation | Kanwar et al. [141] |
| Monoterpenes                 | Isolated compound     | Essential oil of several medicinal plants *(Matricaria recutita, Boswellia carterii, Pelargonium graveolens, Lavandula angustifolia, Citrus limon, Melaleuca alternifolia, Melaleuca viridiflora, Santalum spicatum, Cedrus atlantica, and Thymus vulgaris)* | Hydroxydihydrocarvone, fenchone, α-pinene, (S)-cis-verbolen, piperitenone oxide, α-terpinene, α-terpineol, terpinen-4-ol, α-carveol, menthone, pulegone, geraniol, citral, citronellol, perillyl alcohol, perillic acid, β-myrcene, carvone, limonene, thymol, carvacrol, linalool, linalyl acetate, borneol, l-borneol, bornyl acetate, terpinenol, thymoquinone, thymohydroquinone, 1,8-cineole, l-minthol, menthone, and neomenthol | Terpenoids         | Reduce the expression of NF-κB target gene MUC2                                  | Cassia et al. [142] |
| Mandevilla longiflora        | Hydroethanolic extract| Plant xylopodium | Ellagic acid, hesperidin, luteolin, naringin, naringenin, and rutin | Polyphenol and flavonoids | Decrease the eosinophils, neutrophils, and mononuclear cell migration in BALF and by histopathological analysis. Decrease the IL-4, IL-5, IL-13, IgE, and LTB4 levels | Almeida et al. [143] |
| Product                      | Product form | Product source | Active compound                  | Compound class/type | Mechanism of action                                                                 | Reference |
|------------------------------|--------------|----------------|----------------------------------|---------------------|-------------------------------------------------------------------------------------|-----------|
| *Morus alba* L               | Isolated compound | Root bark        | Moracin M. (5-(6-hydroxy-1-benzofuran-2-yl)benzene-1,3-diol) | Not reported        | Inhibit the PDE4                                                                     | Chen et al. [144] |
| *Haemanthus coccineus*       | Extract      | Dried bulbs      | Narciclasine                      | Alkaloid            | Inhibit the edema formation, the leucocyte infiltration, and cytokine synthesis in vivo. Block the interaction between the leucocyte and endothelial cells, the activation of isolated leucocytes (cytokine synthesis and proliferation) and of primary endothelial cells (adhesion molecule expression) in vitro. Suppress the NF-κB-dependent gene transcription. Attenuates the bronchoconstriction by reduction of calcium influx. | Fuchs et al. [145] |
| Naringin                     | Isolated compound | Common grapefruit | Naringin                          | Flavone             | Attenuates the bronchoconstriction by reduction of calcium influx                     | Wang et al. [146] |
| *Nelumbo nucifera*           | Extract      | Leaves           | Nuiciferine and aporphine         | Alkaloids           | Attenuate the bronchoconstriction by reduction of calcium influx                     | Yang et al. [147] |
| Nigella sativa               | Oil          | Seeds            | Thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone) | Quinone             | Decrease the NO and IgE levels. Increase the IFN-γ                                 | Salem et al. [148]; Koshak et al. [149] |
| Product          | Product form | Product source               | Active compound                                                                 | Compound class/type | Mechanism of action                                                                                                                                                                                                 | Reference                  |
|------------------|--------------|------------------------------|---------------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| NujiangexanthoneA | Isolated compound | Leaves of *Garcinia nuijiangensis* | 1,2,5,6-Tetrahydroxy-3-methoxy-4,7,8-tri(3-methylbut-2-enyl)-xanthone | Xanthone            | Suppresses the IgE/Ag activation and degranulation of mast cell. Suppresses the production of cytokines and eicosanoids, through inhibiting Src kinase activity and Syk-dependent pathways. Inhibits the release of histamine, PGD2 and leukotriene C4 generation. Inhibits the increase of IL-4, IL-5, IL-13, and IgE levels. Inhibits the cell infiltration and increases mucus production. | Lu et al. [150]            |
| Oleanolic acid   | Synthetic compound | *Forsythia viridissima* | Oleanolic acid                                                                 | Triterpenoid        | Modulates the transcription factors T-bet, GATA-3, RORγt, and Foxp3                                                                                                                                             | Kim et al. [151]           |
| Omega 3          | Isolated compound | Fish oil | n-3 Polyunsaturated fatty acid                                              | Fatty acid          | Decreases the IL-17 and TNF-α levels                                                                                                                                                                              | Hansen et al. [152]; Farjadian et al. [153] |
| Organic acids    | Isolated compound | *Berberis integerrima* and *B. vulgaris* fruits | Malic, citric, tartaric, oxalic, and fumaric acids | Organic acids      | Inhibits the Th2 cytokines                                                                                                                                                                                      | Ardestani et al. [154]; Shaik et al. [155] |
| Oroxylin A       | Isolated compound | *Scutellariae radix*        | 5′,7-Dihydroxy-6-methoxy-2phenyl-4H-1-benzopyran-4-one                    | Flavonoid           | Reduces the airway hyperactivity. Decreases the levels of IL-4, IL-5, IL-13 and IgE in BALF                                                                                                                                 | Lu et al. [156]; Zhou et al. [157] |
| Oxymatrine       | Isolated compound | Root of the *Sophora flavescens* Aiton (Fabaceae) | Oxymatrine                                                                 | Alkaloid            | Inhibits the eosinophil migration, IL-4, IL-5, IgE, and IL-13 levels. Inhibits the expression of CD40 protein                                                                                                                                 | Zhang et al. [158]         |
| Product                          | Product form          | Product source          | Active compound                                      | Compound class/type                                      | Mechanism of action                                                                 | Reference            |
|---------------------------------|-----------------------|-------------------------|------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------|----------------------|
| *P. integerrima* Gall and *Pistacia integerrima* stew. *Ex brand* | Methanolic and crude extract | Galls and whole plant | Not reported | Carotenoids, terpenoids, catechins, and flavonoids | Attenuate the TNF-α, IL-4, and IL-5 expression levels, and pulmonary edema by elevation of AQP1 and AQP5 expression levels | Rana et al. [159]; Bibi et al. [160] |
| *Paeonia emodi* royle           | Extract               | Rhizomes                | 1β, 3β, 5α, 23, 24-Pentahydroxy-30-nor-olean-12, 20(29)-dien-28-oic acid; 6α, 7α-epoxy-1α, 3β, 4β, 13β-tetrahydroxy-24, 30-dinor-olean-20-ene-28, 13β-olide; paeonin B; paeonin C; methyl grevillate; 4-hydroxy benzoic acid, and gallic acid | Terpenoids and phenolic compounds | Inhibits the lipoxigenase activity | Zargar et al. [161] |
| *Petasites japonicus*           | Extract               | Leaves                  | Petatewalide B                                       | Not reported                                             | Inhibit the degranulation of β-hexosaminidase in mast cells, the iNOS induction, and the NO production. Inhibits the accumulation of eosinophils, macrophages, and lymphocytes in BALF | Choi et al. [162]    |
| *Peucedanum praeruptorum dunn*  | Extract               | Roots                   | Dihydropyranocoumarin, linear furocoumaris, and simple coumarin | Coumarins | Attenuate the airway hyperreactivity and Th2 responses | Xiong et al. [163] |
| *Peucedani Radix*               | Extract               | Roots                   | Nodakenin, nodakenetin, pteryxin, praeruptorin A, and simple praeruptorin B | Not reported                                             | Inhibit the Th2 cell activation | Lee et al. [164] |
| *Eryngium*                      | Extract               | Leaves, fruits, and roots | A1-barrigenol, R1-barrigenol, tiliroside, kaempferol 3-O-β-D-glucoside-7-O-α-L-rhamnose, rutin, agasyllin, grandivittin, aegelinol benzoate, aegelinol, R′-(+)-rosmarinic (61), and R′-(+)-3′-O-β-D-glucopyranosyl rosmarinic acid | Phenol, flavonoids, tannins, and saponins | Not elucidated | Erdem et al. [165] |
| *Pericampylus glaucus*          | Extract               | Stems, leaves, roots, and fruits | Periglaucine A-D and mangiferonic acid | Alkaloids, terpenoids, isoflavones, and sterols | Inhibit the COX enzymes activity | Shipton et al. [166] |
| Product                          | Product form      | Product source        | Active compound                          | Compound class/type | Mechanism of action                                                                 | Reference |
|---------------------------------|-------------------|-----------------------|------------------------------------------|---------------------|-------------------------------------------------------------------------------------|-----------|
| Aquilaria malaccensis           | Ethanolic extract | Seeds                 | Aquimavitalin                            | Phorbol ester       | Inhibit the mast cell degranulation                                                  | Korinek et al. [167] |
| Phytochemicals                  | Isolated compound | Several medicinal plants | Luteolin, kaempferol, quercetin, eudesmin, magnolin, woorenoside, zerumbone, aucubin, triptolide, nitocine, berberine, and piperine | Flavonoids, lignans, terpenoids, and alkaloids | Suppress the TNF-α expression                                                        | Iqbal et al. [168] |
| Picrasma quassioides (D.Don) Benn | Alcoholic extract | Not reported           | 4-Methoxy-5-hydroxycanthin-6-one         | Alkaloid            | Decreases the inflammatory cell count in BALF. Reduces the IL-4, IL-5, IL-13, and IgE levels. Reduces the airway hyperresponsiveness. Attenuates the recruitment of inflammatory cells and the mucus production in the airways. Reduces the overexpression of inducible nitric oxide synthase (iNOS) | Shin et al. [169] |
| Pinus maritime (Pycnogenol®)    | Extract           | Barks                 | Procyanidin                              | Flavonoid           | Decrease the NO production, the inflammatory cell count, and the levels of IL-4, IL-5, IL-13, and IgE in BALF or serum. Reduces the IL-1β and IL-6 levels, the expression of iNOS and MMP-9. Enhances the expression of heme oxygenase (HO)-1. Attenuates the airway inflammation and mucus hypersecretion | Shin et al. [170] |
| Ping chuan ke li                | Not elucidated    |                       |                                          |                     |                                                                                     | Wang et al. [171] |
| Piperine                        | Isolated compound | *Piper nigrum* (black pepper) and *Piper longum* (long pepper) | Piperine                   | Alkaloid            | Inhibits eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production | Chinta et al. [172] |
| Product                        | Product form       | Product source        | Active compound                                                                 | Compound class/type | Mechanism of action                                                                                                                                                                                                 | Reference          |
|-------------------------------|--------------------|-----------------------|---------------------------------------------------------------------------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Piperlongumine                | Isolated compound | *Piper longum*        | Piperlongumine (5,6-dihydro-1-[(2E)-1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-2(1H)-pyridinone) | Alkaloid            | Inhibits the activity of inflammatory transcription factors, NF-κB, and signal transducer and activator of transcription (STAT)-3 as well as the expression of IL-6, IL-8, IL-17, IL-23, matrix metalloproteinase (MMP)-9, and intercellular adhesion molecule (ICAM)-1. Suppresses the permeability and leukocyte migration, the production of TNF-α, IL-6, and extracellular regulated kinases (ERK) 1/2 along with the activation of NF-κB                                                                 | Prasad and Tyagi [173] |
| *Piper nigrum*                | Ethanolic extract  | Not reported          | Piperine                                                                         | Alkaloid            | Inhibit the Th2/Th17 responses and mast cell activation                                                                                                                                                                                                                     | Bui et al. [174]; Khawas et al. [175] |
| *Plectranthus amboinicus*     | Ethanol, methanol, and hexane extracts | Aerial parts | Rosmarinic acid, shimobashiric acid, salvianolic acid L, rutin, thymoquinone, and quercetin | Flavonoids          | Not elucidated                                                                                                                                                                                                                                                                  | Arumugam et al. [176] |
| *Podocarpus sensu latisimo*   | Extract            | Barks                 | 3-Methoxyflavones and 3-O-glycosides                                            | Flavonoids          | Provinol and flavin-7                                                                                                                                                                                                                                                        | Abdillahi et al. [177] |
| Polyphenols and their compounds | Isolated compound  | Provinol and flavin-7 | Quercetin and resveratrol                                                        | Polyphenol          | Decrease IL-4 and IL-5 levels, the airway hyperresponsiveness, and mucus overproduction                                                                                                                                  | Joskova et al. [178] |
| Propolis                      | Isolated compound  | Honey bees from several plants | Pinocembrin and caffeic acid phenethyl ester                                      | Polyphenol and terpenoids | Inhibits TGF-β1                                                                                                                                                                                                                                                                | Kao et al. [179] |
| *Psoralea corylifolia*        | Extract            | Fruits                | 7-O-Methylcorylifol A, 7-O-isoprenykcorylifol A, and 7-O-isoprenylneobavaisoflavone | Flavonoids          | Inhibit the N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP)-induced O$_2^-$ generation and/or elastase release                                                                                                                                                           | Chen et al. [180]  |
| Product                     | Product form | Product source          | Active compound                                                                 | Compound class/type | Mechanism of action                                                                                                                                                                                                 | Reference                      |
|-----------------------------|--------------|-------------------------|---------------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Quercetin                   | Isolated compound | Tea, fruits and vegetables | 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one | Flavonoid           | Inhibits LOX and PDE4. Reduce leukotrienes and histamine release with a decrease in the IL-4 level. Inhibit prostaglandins release and the human mast cell activation by Ca2+ influx.                             | Townsend et al. [181]; Mlcek et al. [182] |
| Radix Rehmanniae Preparata  | Extract      | Not reported            | Catalpol                                                                       | Glycoside           | Inhibit IgE secretion. Decrease IL-4 and IL-5. Inhibit eosinophil infiltration and suppress eotaxin and its receptor CCR3. Reduce IL-5RA levels.                                                                          | Chen et al. [183]               |
| Resveratrol                 | Isolated compound | Skin and barks of red fruits | Resveratrol (3,4,5-trihydroxystilbene)                                        | Polyphenol          | Decreases eosinophilia. Reduce neutrophil migration and inhibit PGD-2 release. Decrease IL-4 and IL-5 and also the hyperresponsiveness and mucus production                                                         | Lee et al. [184]; Hu et al. [185]; Chen et al. [186] |
| Schisandra chinensis        | Extract      | Dried fruits            | α-Cubebenoate                                                                  | Not reported        | Suppress bronchiolar structural changes. Inhibit the accumulation of lymphocytes, eosinophils, and macrophages in BALF. Suppress IL-4, IL-13, and TGF-β1. Increase the intracellular Ca2+                                                   | Lee et al. [187]               |
| Sea cucumber (Holothurians) | Tonic        | Marine animal (Sea cucumber) | Holothurin A3, pervicoside A, and fuscocinersides A | Toxins              | Reduce COX enzymatic activity                                                                                     | Guo et al. [188]               |
| Product                          | Product form       | Product source     | Active compound                                      | Compound class/type | Mechanism of action                                                                 | Reference               |
|---------------------------------|--------------------|--------------------|------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------|------------------------|
| **Selaginella uncinata** (Desv.)| Extract            | Dried herbs        | Amentoflavone, hinokiflavone, and isocryptomerin     | Flavonoids          | Attenuate hyperresponsiveness and goblet cell hyperplasia. Decrease IL-4, IL-5, IL-13, and IgE levels in serum. Upregulation of T2R10 gene expression and downregulation of IP3R1 and Orai1 gene expression. Suppression of eotaxin, NFAT1, and c-Myc protein expression | Yu et al. [189]         |
| **Selaginella pulvinata**        | Isolated compound  | Air-dried powder of the whole plant of S. pulvinata | Selaginpulvinin A, selaginpulvinin B, and selaginpulvinin C | Phenol              | Inhibit the PDE4                                                                     | Liu et al. [190]        |
| **Sideritis scardica**           | Extract            | Leaves             | Echinacoside, verbascoside, luteolin, apigenin, caffeic acid, vanillic acid | Glycosides, flavonoids, and phenolic acids | Not elucidated                                                                      | Todorova and Trendafilova [191] |
| **Siegesbeckia glabrescens**     | Extract            | Aerial roots       | 3,4-O-Dimethylquercetin, 3,7-O-dimethylquercetin, 3-O-methylercetin, and 3,7,40-O-trimethylquercetin | Flavonoids          | Reduce inflammatory cell infiltration in BALF. Decrease IL-4, IL-5, IL-13, eotaxin, and IgE. Reduce airway inflammation and mucus overproduction. Decrease iNOS and COX-2 expression and reduce NO levels | Jeon et al. [192]        |
| **Sitostanol**                   | Isolated compound  | Marketable synthetic compound | Sitostanol                                            | Steroid             | Suppresses IL-4 and IL-13 release                                                   | Brüll et al. [193]      |
| **Soft coral**                   | Isolated compound  | Sarcophyton ehrenbergi | Not reported                                          | Prostaglandins      | Inhibits PDE4                                                                        | Cheng et al. [194]      |
| **Solanum paniculatum** L        | Extract            | Fruits             | Stigmasterol and β-sitosterol                         | Steroid             | Reduce IL-4 and NO levels. Decrease IFN-γ without changes in IL-10 levels. Reduce NF-κB, TBET, and GATA3 gene expression | Rios et al. [195]       |
| **Squill (Drimia maritima** (L.) stern) oxymel | Crude extract     | Not reported       | Scillaren A, scillirubroside, scilliroside, scillarenin, and proscillaridin A | Glycosides          | Not elucidated                                                                      | Nejatbakhsh et al. [196] |
| Product                          | Product form       | Product source | Active compound                                                                 | Compound class/type | Mechanism of action                                                                                                                                                                                                 | Reference     |
|---------------------------------|--------------------|----------------|---------------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| *Sorbus commixta* Hedl. (Rosaceae) | Methanolic extract | Fruits         | Neosakuranin                                                                   | Glycosides          | Reduce nitric oxide production and reduce the relative mRNA expression levels of inducible nitric oxide synthase (iNOS), IL-6, cyclooxygenase-2, MMP-9, TNF-α in vitro. Decrease the inflammatory cell counts in BALF. Reduce IL-4, IL-5, IL-13, eotaxin, and IgE levels and reduce the airway hyperresponsiveness, in vivo. Attenuate mucus hypersecretion | Bhatt et al. [197] |
| *Thuja orientalis*              | Extract            | Fruits         | Cupressuflavone, amentoflavone, robustaflavone, afzelin, (+)-catechin, quercetin, hypolaetin 7-O-β-xylopyranoside, isoquercitrin, and myricitrin | Flavonoids          |                                                                                                                                                                                                                      | Shin et al. [198] |
| Tonggyu-tang                    | Extract            |                | Not reported                                                                    | Plant               | Inhibit inflammatory cytokines (IL-4, IL-6, IL-8, and TNF-α). Suppress mitogen activated protein kinase (MAPK) and NF-κB in mast cells and keratinocytes                                                                                                                                 | Kim et al. [199] |
| Product                        | Product form | Product source | Active compound                                      | Compound class/type | Mechanism of action                                                                 | Reference                  |
|-------------------------------|--------------|----------------|------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------|----------------------------|
| *Trigonella foenum-graecum*   | Extract      | Seeds          | Not reported                                         | Flavonoids          | Reduce IL-5, IL-6, IL-1β, and TNF-α. Reduce collagen deposition in goblet cells. Suppress inflammatory cells | Piao et al. [200]          |
| *Tropidurus hispidus*         | Oil          | Fat of *Tropidurus hispidus* | Croton oil, arachidonic acid, phenol, and capsaicin | Fatty acids and its derivated | Affect the arachidonic acid and their metabolites and reduce proinflammatory mediators | Santos et al. [201]        |
| *Urtica dioica*               | Extract      | Leaves         | Caffeic acid, gallic acid, quercetin, scopoletin, carotenoids, secoisolariciresinol, and anthocyanidins | Polyphenols, flavonoids, cumarin, and lignan | Reduce leucocytes and lymphocytes levels in serum. Inhibit the eosinophilia increase in BALF. Suppress inflammatory cells recruitment and attenuation of lipid peroxidation of lung tissues | Zemmouri et al. [202] |
| Verproside                    | Isolated compound | Pseudolysimachion | Verproside                                           | Glycoside           | Suppress the NF-κB and TNF-α expression                                               | Lee et al. [203]           |
| Vitamin D                     | Isolated compound | Not reported   | Calcitriol                                           | Vitamin             | Inhibit lymphocytes (Th1 and Th2) and reduces cytokines production                   | Szekely and Pataki [204]  |
| Vitamin E                     | Isolated compound | Plant lipids   | α-, β-, γ-, and δ-Tocopherols and the α-, β-, γ-, and δ-tocotrienols | Vitamin             | Reduce airway hyperresponsiveness, IL-4, IL-5, IL-13, OVA-specific IgE, eotaxin, TGF-β, 12/15-LOX, lipid peroxidation, and lung nitric oxide metabolites | Cook-Mills and McCary [205]; Abdala-Valencia et al. [206] |
| *Vitex rotundifolia*          | Methanolic extract | Fruits         | 1H, 8H-Pyran [3, 4-c]pyran-1,8-dione                  | Not reported        | Inhibit eotaxin, IL-8, IL-16, and VCAM-1 mRNA                                         | Lee et al. [207]           |
| *Viticis fructus*             | Extract      | Dried fruit    | Pyranopyran-1,8-dione                                | Not reported        | Inhibit eosinophils and lymphocytes cell infiltration into the BAL fluid. Reduce to normal levels of IL-4, IL-5, IL-13 and eotaxin. Suppress IgE levels | Park et al. [208]          |
| Product                  | Product form | Product source                                                                 | Active compound                                                                 | Compound class/type                  | Mechanism of action                     | Reference                     |
|-------------------------|--------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------|-----------------------------------------|-------------------------------|
| Yu ping feng san        | Extract      | Radix Saposhnikoviae (Fangfeng), Radix Astragali (Huangqi), and Rhizoma Atractylodis macrocephalae (Baizhu) | Calycosin-7-O-β-d-glucoside, calycosin, formonetin, atracylenolide III, II, and I; 5-O-methylvisammioside, 8-methoxyxpsoralen and bergapten | Flavonoids, terpenoids, saponins, and furocoumarins | Inhibit TNF-α, IFN-γ, and IL-1β       | Stefanie et al. [209]          |
| Zygophyllum simplex L   | Extract      | Aerial parts                                                                    | Isorhamnetin-3-O-β-D-rutinoside, myricitrin, luteolin-7-O-β-D-glucoside, isorhamnetin-3-O-β-D-glucoside, and isorhamnetin | Phenol                                | Inhibit NF-κB, TNF-α, IL-1β, and IL-6   | Abdallah and Esmat [210]        |
| Ziziphus amole          | Extract      | Leaves, stems, barks, and roots                                                 | Alphitolic acid, sitosterol, ziziphus-lanostan-18-oico acid                     | Terpenoid and steroid                 | Inhibit myeloperoxidase activity       | Romero-Castillo et al. [211]   |
between C2 and C3 indicates flavones and isoflavones, and the addition of a C1 to C2 double bond represents anthocyanidins [214].

The diversity in their chemical structure contributes to their broad range of physiological and biological activities, from which it can be highlighted the antioxidant, anti-inflammatory, antiallergic, antiviral, hepatoprotective, antithrombotic, and anticarcinogenic activities [213]. In this review, 14 studies reported flavonoids as a group of compounds able to be used on asthma treatment. The following subsections show the main flavonoids with antiasthmatic activity reported in the literature and used by the traditional medicine. These studies attributed the antiasthmatic activity of plant extracts containing these compounds, in part, due to their presence in the phytocomplex.

(1) Flavone Compounds: Chrysin, Baicalin, Luteolin, and Oroxylin A. Defined as 5,7-dihydroxy-2-phenyl-1-H-chromen-4-one, chrysin is classified as a flavone that can be found in Passiflora caerulea and Passiflora incarnate flowers, as well as in Matricaria chamomilla, popularly known as chamomile, besides being present in propolis and other plants [90, 100]. Chrysin is a compound able to suppress the proliferation of airway smooth muscle cells as well as to promote a reduction in the IL-4, IL-13, IgE, and interferon-γ levels that lead to an attenuation in the asthma inflammatory process [89]. Bae et al. [90] performed their studies through an in vitro cell culture model with the purpose to describe how the chrysin was able to promote the inhibitory effect in the proinflammatory cytokines. They suggested that this effect was caused by the intracellular calcium reduction in mast cells, since calcium is responsible for proinflammatory cytokine gene transcription [90]. In addition, a study performed by Yao and colleagues [88] investigated the activity of chrysin against asthma in mice sensitized with ovalbumin (OVA). Their results revealed that chrysin would be a promising compound able to be used for controlling airway remodeling and clinical manifestations of asthma [88].

Baicalin, a 7-glucuronic acid-5,6-dihydroxyflavone, is a natural metabolite easily found in leaves and barks from several species of the Scutellaria genus [215]. Studies performed by Park and colleagues [208] investigated the anti-inflammatory activity of baicalin using an asthma-induced animal model. The results showed that this compound decreased the inflammatory cell infiltration and the levels of TNF-α in the bronchoalveolar lavage fluids (BALF). The activity of the baicalin was attributed to the fact that this metabolite selectively inhibits the enzyme activity of PDE4 and suppresses the TNF-α expression induced by the lipopolysaccharides on macrophages, indicating a potential use of this metabolite in asthma treatment [74].

Additionally, luteolin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-chromenone), another compound that had also demonstrated antiasthma activity, is widely found in aromatic flowering plants, such as Salvia tomentosa and Lamiaceae, as well as in broccoli, green pepper, parsley, and thyme [216]. Shen and colleagues [133] studied its pharmacological activity through inhibition of the GABAergic system, which is responsible for the overproduction of mucus during the asthmatic crisis by overstimulation of the epithelial cells. The study indicated that this compound was able to promote the attenuation of the goblet cell hyperplasia by the partial inhibition of GABA activities [133].

Another antiasthmatic flavonoid compound is oroxylin A, a flavone found in the extract of Scutellaria baicalensis Georgi and Oroxyllum indicum tree [156]. According to Zhou [157], oroxylin A, or 5,7-dihydroxy-6-methoxy-2-phenyl-chromen-4-one, was able not only to reduce the airway hyperactivity in an OVA-induced asthma murine model, but also to decrease the levels of IL-4, IL-5, IL-13, and OVA-specific IgE in BALF [157]. This study also showed the ability of oroxylin A in inhibiting the alveolar wall thickening in addition to avoid the inflammatory cell infiltration in the perivascular and peribronchial areas assessed by histopathological evaluation [157].

(2) Flavonol Compounds: Quercetin, Galangin, and Kaempferol. Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one), a flavonol compound widely found in onions, apples, broccoli, cereals, grapes, tea, and wine, has been known as the main active compound of these plants and, therefore, responsible for their widespread use in traditional medicine for the treatment of inflammatory, allergic, and viral diseases [213]. The studies using this compound as antiasthma were performed in cell cultures and rats, as in vitro and in vivo models, respectively, showing its high capacity to reduce inflammatory processes. According to these studies, the anti-inflammatory mechanism of quercetin is attributed to the lipoxygenase and PDE4 inhibition and reduction on histamine and leukotriene release, which promote a decrease in the proinflammatory cytokine formation and production of IL-4, respectively. In addition, quercetin also promoted the inhibition of human mast cell activation by Ca²⁺ influx and prostaglandin release inhibition [182], favoring the therapeutic relief of the asthma symptoms and decreasing the short-acting β-agonist dependence [181, 182].

Galangin, a compound chemically defined as 3,5,7-trihydroxy-2-phenylchromen-4-one, easily found on Alpinia officinarum [217], had its pharmacological activity evaluated using a specific-pathogen-free mice model [115]. The study, performed by Liu [115], showed an effective response against the in vivo OVA-induced inflammation as well as a reduction on the ROS levels in vitro. Furthermore, galangin acted as an antiremodeling agent in asthma, since this compound inhibited the goblet cell hyperplasia, lowering the TGF-β1 levels and suppressing the expression of vascular endothelial grown factor (VEGF) and matrix metalloproteinase-9 (MMP-9) in BALF or lung tissue. This result highlighted its antiremodeling activity in the TGF-β1-ROS-MAPK pathway, proving its potential use on asthma treatment [115].

Another flavonol, kaempferol, chemically defined as 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one, is widely found in citrus fruits, broccoli, apples, and other plant sources [213]. This compound has been studied due to its pharmacological potential, especially against
inflammation. In the study performed by Chung et al. [127], an OVA-induced airway inflammation mouse model of asthma was performed, demonstrating that kaempferol can significantly reduce the inflammatory process due to the decrease of the inflammatory cell infiltration and the decrease of production of inflammatory cytokines and IgE antibodies. In addition, this compound was also able to reduce the intracellular ROS production in the airway inflammation reaction [127].

Furthermore, Mahat et al. [218] demonstrated that the anti-inflammatory activity of kaempferol occurs through the inhibition of nitric oxide and nitric oxide-induced COX-2 enzyme activation, further inhibiting the cytotoxic effects of nitric oxide, reducing the prostaglandin-E2 production [218]. To improve the possibility of the use of kaempferol as a bioactive on the development of new drugs or medicines, the previously mentioned study by Chung [127] also describes the antiasthma activity of a glycosylated derivative of kaempferol, the kaempferol-3-O-rhamnoside. The glycosylation of kaempferol improved its solubility and stability, besides reducing its toxicity [127], allowing the production of a compound with great potential to increase the asthma therapeutic arsenal. According to this rationale, this compound may be responsible for the anti-inflammatory properties of the plant extracts containing this substance and that have been used to asthma treatment.

2.1.2. Resveratrol. Resveratrol is a natural stilbenoid compound, a class of polyphenol obtained from the bark of red fruits, with known antioxidant and promising anti-inflammatory and antiasthma activities [186]. In studies using eosinophils obtained from asthmatic individuals, Hu et al. [185] demonstrated that resveratrol induces not only cell cycle arrest in the G1/S phase, but also apoptosis, allowing a decrease in the eosinophil number [185], thus reducing the neutrophil migration and, consequently, preventing the histamine and PGD-2 release, avoiding vasodilatation, mucus production, and bronchoconstriction (Figure 1). Additionally, Lee and colleagues [129] demonstrated that resveratrol was effective against the asthmatic mouse model once this polyphenol induced a significant decrease in the plasma level of T-helper-2-type cytokines, such as IL-4 and IL-5. It also decreased the airway hyperresponsiveness, eosinophilia, and mucus hypersecretion [184]. Although performed by different methods, the studies are in agreement regarding the scientific evidence that supports the use of resveratrol by oral route as an effective natural compound to treat asthma patients.

2.1.3. Boswellia. Boswellia is a tree genus that produces oil known as frankincense, which is obtained through incisions in the trunks of these trees. This oil is composed by 30–60% resin, 5–10% essential oils, and polysaccharides [219]. Studies performed using this product evaluated its pharmacological activities revealing that the Boswellia bioactives are boswellic acids and AKBA (3-O-acetyl-11-keto-β-boswellic acid), both responsible for preventing NF-κB activation and, consequently, inhibiting IL-1, IL-2, IL-4, IL-6, and IFN-gamma release [52]. They also inhibit LOX-5, thus preventing leukotriene release [78]. Thus, based on the physiopathology of asthma, it is possible to infer that these compounds may act as antiasthma molecules from the tree genus, once these enzymes and mediators are involved in the asthma-related inflammation. Moreover, another study that aimed at evaluating the antiasthma activity of these compounds showed that the association between Boswellia serrata, Curcuma longa, and Glycyrrhiza had a pronounced effect on the management of bronchial asthma [79], suggesting its potential on asthma therapy.

2.2. Natural Products from Animal Source. Animal-derived natural products still represent the minority of natural sources for products intended for asthma treatment. Nonetheless, many studies describe the use of animal-based products, such as oils, milk, and spleen as a complementary therapy for several diseases, including asthma. The traditional medicine reports the benefits of consuming some animal parts and animal products, once they can be rich in compounds such as lipids, prostaglandins, unsaturated fatty acids, enzymes, and polysaccharides, which are responsible for their pharmacological activities [220, 221]. In addition, animal sources are also widely cited as biocompatible and biodegradable sources, suggesting their safe use. The animal products and compounds cited in this session can be obtained from several sources, such as mammals, amphibians, and crustaceans, demonstrating its wide range of possibilities.

2.2.1. Animal Sea Source: Holothuroidea, Penaeus, and Sarcophyton ehrenbergii. Marine ecosystems represent an important source of natural compounds due to their wide biodiversity, which include animals and plants that are unique to this environment. Therefore, many studies have been performed to evaluate the antimicrobial, anti-inflammatory, antiviral, and antiasthmatic potential of algae and sea animals.

On this concern, the sea cucumber, a marine invertebrate animal that belongs to the class Holothuroidea, usually found in the benthic areas and deep seas, has been used by Asian and Middle Eastern communities in the traditional medicine as elixir, due to its pharmacological activity on the treatment of hypertension, asthma, rheumatism, cuts, burns, and constipation [188]. These pharmacological activities are attributed to the presence of saponins, cerebrosides, polysaccharides, and peptides on its composition [188, 220]. Bordbar et al. [220], in a literature review, mentioned an experimental study from Herencia et al. [222] in which sea cucumber extract showed a reduction of the enzymatic activity of cyclooxygenase in inflamed mice tissues, without promoting any modification on the cyclooxygenase enzyme, showing that the sea cucumber extract is a potent natural product able to be used against several inflammatory diseases [220].

Ozdemir and colleagues [87] investigated the pharmacological activity of chitin, a polysaccharide formed by repeated units of N-acetylglucosamine to form long chain
through β-(1–4) linkage [221], the major compound of the shrimp (Penaeus) exoskeleton. In this study, the authors performed the intranasal administration of chitin microparticles in the asthma-induced mice model, which promoted the reduction of serum IgE and peripheral blood eosinophilia, besides the decrease of the airway hypersensitivity [87]. Additionally, another study identified and isolated ten new prostaglandin derivatives from the Sarcoophyton ehrenbergi extract, a soft coral species found in the Red sea [194], from which five of them showed inhibitory activity against PDE4 (44.3%) at 10 μg.mL⁻¹, suggesting its utilization on asthma and chronic obstructive pulmonary disease treatment, once PDE4 is the drug target on the treatment of both diseases [194].

Finally, these studies demonstrated that marine source needs to be further investigated, since a wide variety of bioproducts and/or bioactives with potential anti-inflammatory activity and antiasthmatic proprieties can be found in this environment.

### 2.2.2. Bullfrog (Rana catesbeiana Shaw) Oil

The bullfrog oil is a natural oil extracted from the adipose tissue of the amphibian Rana catesbeiana Shaw, which is originated from North America and has its meat widely commercialized around the world [223]. This oil has been used by the traditional medicine to treat inflammatory disorders, especially asthma [223]. This oil is composed of a mixture of monounsaturated fatty acids and bile-derived steroid compound (ethyl iso-allocholate) [81, 224], which are responsible for its therapeutic properties [81].

According to Yaqoob [57], the presence of oleic, linolenic, stearic, palmitic, and myristic fatty acids can promote the suppression of immune cell functions [58]. Based on such evidence, it is possible to infer that the bullfrog oil, due to its chemical composition, can be used on the treatment of inflammation-related disorders such as asthma. However, further studies are needed to confirm this hypothesis.

### 2.2.3. Other Products Derived from Animals

Although the majority of the currently used animal products by the traditional medicine for asthma treatment belong from animal tissues, there is evidence that mammal fluids, for example, buffalo spleen liquid, milk, and colostrum, can act on the immune system promoting the decrease of asthma symptoms [80].

The buffalo spleen liquid was investigated in a study performed by Neamati and colleagues [80], in which pigs were asthma sensitized using ovalbumin, followed by administration of the buffalo spleen liquid-based adjuvant. A decrease in the tracheal response as well as a reduction in the white blood cell number in lung lavage was observed on sensitized animals when compared to healthy animals [80], showing the potentiality of this fluid in promoting asthma control. In addition, another study was performed to evaluate the antiasthma activity using milk and colostrums, which contain linolenic acid and proteins like lactoferrin [141], as a natural product. This study showed a modulation in the plasma lipid concentration in human and animal models and a decrease in the allergic airway inflammation induced by ragweed pollen grain extract.

### 2.3. Bioactives Obtained from Microorganisms

The use of bacteria and fungi metabolites on the treatment of several diseases is widely reported since the penicillin discovery. However, more recent studies have further investigated the antiasthmatic potential of these metabolites [225]. On this concern, a study performed by Lu and colleagues [156] evaluated the antiasthma activity of the bacterial lysate OM-85 Broncho-Vaxom (BV), a patented pharmaceutical product [134]. The study observed that the bacterial lysate coupled with the conventional treatment was able to increase the rate of natural killer T cells on the peripheral blood, decreasing the cytokine level (cytokines type not described) and, then, promoting the reduction of asthma symptoms. Furthermore, kefir, a fermented milk drink produced by lactic and acetic acids from bacteria, which also presents the kefiran, an insoluble polysaccharide as main component [128, 129], had its in vivo anti-inflammatory activity evaluated. This compound was able to reduce at normal levels the release of IL-4, IL-6, and IL-10 along with the production of INF-γ and TNF-α [128]. In addition, the intragastric administration of kefiran promoted the reduction of OVA-induced cytokine production in a murine asthma model, decreasing the pulmonary eosinophilia and mucus hypersecretion [128, 129].

Therefore, based on these reports and historical facts regarding the use of microorganisms as source for isolation of new bioactives and the development of medicines, it is important to highlight that these new agents may contribute to the current asthma treatment.

### 3. Conclusion: Widely Used Active Pharmaceutical Ingredients from Natural Source

As previously demonstrated, natural products have been extensively used as a complementary treatment for asthma therapy. Studies concerning these products have aimed at investigating their activity as a matrix of compounds to complement or replace current asthma treatment, while others aim at isolating compounds to generate new medicines based on synthetic drugs of natural origin [226].

Historically, natural products have contributed tremendously to the development of marketable medicines to the treatment of several diseases [226]. The evaluation of their therapeutic activities and identification and isolation of their bioactive molecules allowed not only their clinical use, but also the discovery of the pharmacophore groups and the radicals responsible for their toxicity or their biopharmaceutics aspects. In fact, based on such studies, it is possible to perform structural or delivery changes on these compounds that would increase their safety or would be able to module their half-life allowing to target them to specific action sites [227].

This review shows the experimental studies that identified the antiasthma activity of different natural sources in
the last decade, along with the molecules responsible for that. Altogether, these studies presented preliminary data that require further investigations about these compounds in order to, in a near future, be used on the production of designing medicines. Currently, a few natural-based active compounds are already available in the market, such as ipratropium bromide, theophylline, epinephrine, and sodium cromoglycate [226, 228–231].

Ipratropium bromide, an anticholinergic drug able to promote bronchodilation, has been widely used for the treatment of asthma. This compound was synthesized from atropine, a compound extracted for the first time in 1809 from Atropa belladonna L. However, it can also be found in other plants from the Solanaceae family [228, 229]. In spite of that, only in 1833, its chemical structure was elucidated, and in 1850, it was implemented for clinical use, allowing the proper understanding of its in vivo biopharmaceutics and therapeutic characteristics [232].

Theophylline is an antiasthmatic drug widely used in the management of severe persistent asthma, promoting the bronchodilation and attenuation of asthma inflammation. Also known as 1,3-dimethylxanthine, this molecule was extracted in 1888 from Theobroma cacao L. and Camellia sinensis L., plants presented in several countries. Later in 1922, this drug was introduced on asthma therapy [233]. Years after, epinephrine, also known as adrenaline, was extracted from the Ephedra sinica, a plant widely used in the Chinese traditional medicine, allowing the synthesis of beta-agonist antiasthmatic drugs, such as salbutamol and salmeterol, currently used in asthma treatment [226].

Furthermore, sodium cromoglycate, a drug obtained from the khellin bioactive extracted from Ammi visnaga (L) Lamk, has been used as a bronchodilator based on its ability of inhibiting mast cell degranulation, which enabled its use on the asthma treatment [226, 230].

Overall, these reports highlight the relevance of the investigation and isolation of new bioactive compounds that could present antiasthmatic potential. As the current asthma treatment involves drugs that have been extensively studied in the past decades, the experimental studies that evaluate the activity of compounds obtained from diverse natural sources might allow the development of new antiasthmatic drugs in the near future.

4. Final Considerations

The current asthma treatment is of high cost and has many side effects, which compromises the patient treatment compliance. Literature reports show that asthma treatment can be improved using natural products to complement the traditional drugs, since those products are of low cost and biocompatible and show reduced side effects. The literature search included the keywords asthma, natural products, and treatment, individually, resulted in 14,296,762 studies, including scientific articles, reviews, editorial reference works, and abstracts. Additionally, the keyword combination “Asthma + Natural Products” found 18,111 studies, “Asthma + Treatment,” 209,423 studies, “Natural Products + Treatment,” 459,685 studies, and “Asthma + Treatment + Natural Products,” 1,986 studies. Thus, after screening for duplicate studies, 1,934 abstracts were evaluated. Finally, based on the inclusion criteria, 172 studies reporting the use of natural products on asthma treatment were included in this review, summarizing a total of 160 studies that reported plants as natural source, 9 from animal source, and 3 studies describing bacteria and fungi as bioactive sources, totaling 134 compounds which can be used as complementary or alternative medicine on asthma treatment. Plants were found to be the major source of products used by the folk medicine to treat asthma, since they are a renewable source of easy access. Also, due to their variety of secondary metabolites, plants are able to promote antiasthmatic activity mainly due to their anti-inflammatory and bronchodilator properties. This study revealed that flavonoids, phenolic acids, and terpenoids are the main elucidated compounds able to promote the attenuation of asthma symptoms. On the other hand, a lack of scientific reports regarding the pharmaceutical activity of natural products from animal and microorganism sources has limited their use. However, these products still represent an important source of bioactive compounds able to be used on asthma treatments. In addition, despite the relevant antiasthmatic activity, the literature search showed a lack of investigations concerning the pharmacokinetics properties as well as more accurate information regarding efficacy, safety, and the required dosage to induce in vivo antiasthma activity. In conclusion, due to the fact that current asthma treatment involves drugs obtained from natural products widely explored in the past, the current experimental studies reported in this review may lead to the development of new drugs in the future, able to improve the antiasthmatic treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

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