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Revolutionizing Asthma Management: An Overview of Recent Advancements in Treatment, Personalised Medicine and Biologic Therapies

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A B S T R A C T:

A frequent yet complicated heterogeneous inflammatory airway disease is asthma. Even with great advancements in our knowledge of the pathogenesis and management of asthma, the condition still accounts for a large portion of death and morbidity. The best course of treatment includes addressing modifiable risk factors, carefully titrating inhaled medication, and, in cases of severe illness, considering biologic medicines. The establishment of more precise phenotypic and endotypic subgroups of asthma has been made possible by an appreciation of the clinical features of the condition and an understanding of the immunological mechanisms involved. This has completely changed the way that asthma is managed by enabling risk assessment of patients, focused use of biologic drugs to alter the cytokine reactions that trigger asthma attacks, and enhanced patient results. In an age where patient involvement and education are essential to the management of this illness. This review centers on new developments in severe and uncontrolled asthma, both clinically and translationally, which open the door to phenotyping and tailored treatments for these patients. While asthma is widespread in both adults and children and usually responds to normal medications, some people with asthma continue to have severe symptoms even after receiving the right therapy. The hallmark of severe asthma is airflow restriction that frequently results in symptoms that need larger dosages of controller medication; however, the underlying biological mechanisms, or endotypes, vary widely across individuals.

Keywords: Asthma, Traditional, Personalized, Biologic, Diseases, Inflammatory

1. Introduction

A chronic respiratory condition that affects millions of individuals worldwide is asthma. Significant advancements in treatment choices have occurred in recent years, improving patients' quality of life and enabling better symptom management.[1] The chronic respiratory disease known as asthma is characterized by airway constriction and inflammation. Breathlessness, wheezing, and coughing are some of the symptoms. Exercise, stress, and allergies can all cause asthma episodes. When someone is diagnosed with asthma, their clinical course varies greatly. Remission is frequent, with children experiencing remission at higher rates than adults.[2-4] A lower FEV1, female sex, and recent onset of symptoms are among the pertinent clinical characteristics linked to the duration of asthma symptoms.[5] Therapy-resistant asthma was described in 1999 by the European Respiratory Society[6] as evidence of blockage or persistent symptoms after months of effective guideline-based asthma care. The American Thoracic Society and the European Respiratory Society jointly released an amended definition of asthma that now includes severe asthma, which is defined as asthma that requires both a second controller medication and high-dose inhalation corticosteroids (ICSs). At 5% to 10% of all asthma patients, persistent and severe asthma often coexist and account for a significant amount of asthma resources overall.[7]

Assessment of Asthma and Related Conditions

1.1 Asthma Diagnosis

While cough, wheeze, and intermittent dyspnea are often linked to asthma, these symptoms are vague and frequently manifest as atypical asthma symptoms.[8] Thus, regardless of the presence of classical symptoms, asthma should be suspected, and even in patients who exhibit classical symptoms, a diagnosis of another non-asthma condition should be explored.Reversible airflow restriction is one example of an objective measurement that can be used to support an asthma diagnosis, even though the diagnosis is dependent on clinical evidence.Numerous organizations have released guidelines for the diagnosis of asthma in both adults and children.[9-10] The importance of a thorough history is emphasized by these guidelines, which also include noting common triggers, occupational exposures, personal histories of wheezing, exercise-induced symptoms, and family histories of asthma symptoms. Spirometry should be used in patients older than five to assess the bronchodilator response, and bronchoprovocation testing should be considered in kids

who do not have airflow blockage. Other diagnoses must be taken into account, especially when there is severe or ongoing asthma. Auscultation may indicate an upper airway blockage, which can be differentiated from asthma with spirometry and otolaryngologic examination. On the other hand, spirometry patterns associated with asthma can be mimicked by COPD, bronchiectasis, bronchiolitis obliterans, sarcoidosis, and lower airway obstruction due to masses or foreign objects. Persistent dyspnea, especially in the absence of other asthma symptoms, should be evaluated thoroughly; typical causes of persistent dyspnea include cardiovascular illness, obesity, and anemia. Interstitial lung disease should also be taken into account, especially in hypoxic environments. Although it was long understood that asthma might be the source of a persistent cough without accompanying wheezing or dyspnea, other common causes of coughing up mucus include acute or chronic infections, acid reflux, aspiration, and interstitial lung disease.[11] Because some over-the-counter and prescription drugs might exacerbate asthma symptoms, it is important to carefully assess medication usage. While these factors typically apply to both adults and children, immunodeficiency, cystic fibrosis, and foreign body aspiration are of special concern in children.[12] For the purpose of ruling out other possible diseases and confirming the diagnosis of asthma, bronchoscopy with BAL, endobronchial biopsies, transbronchial biopsies, and/or endobronchial ultrasound-guided biopsies of lymph nodes should also be taken into consideration in cases of severe asthma.

1.2 Comorbid Diseases

Patients with asthma frequently have coexisting medical conditions, which can significantly exacerbate asthma symptoms. More than half of children with asthma have allergic rhinitis, and it is more common in asthmatic adults and children than in non-asthmatic ones. In a particular cohort, it was found in 82% of nonsmoker adults with severe asthma.[12–13] Asthma and allergic sensitization often co-occur, especially in children. Lung residual volume and obesity are inversely correlated, which can make asthmatic patients' dyspnea symptoms worse. Nevertheless, obese patients also have altered inflammatory states in their adipose tissue, lung immune cells, and lung, including elevated levels of proinflammatory molecules like IL-6, leptin, and tumor necrosis factor-alpha.[14–16] Patients with asthma should also have the existence of OSA taken into account. Another prevalent disorder that exacerbates asthma symptoms in adults and children alike is gastroesophageal reflux disease. Asthma-COPD overlap syndrome is the coexistence of asthma and COPD in persons who have smoked.[17]

1.3 Asthma-Associated Diseases

Apart from the previously mentioned concomitant conditions, a number of illnesses also aggravate asthma symptoms but are linked to asthma and infrequently manifest without asthma. In individuals with persistent asthma, far higher percentages have been found, reaching as high as 38.6% in patients with acute severe asthma exacerbations. Allergic bronchopulmonary aspergillosis affects 1% to 2% of asthma patients.[18–19] Antibodies specific to Aspergillus and increased IgE levels are linked to this disease. In clinical practice, patients often present with mucoid impaction and may expectorate airway casts; chest radiographs may show migrating or transitory opacities. In the context of asthma, aspirin sensitivity and chronic rhinosinusitis with nasal polyposis have been characterized as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory diseases, which typically cause bronchospasm a few hours after NSAID or aspirin consumption. A long history of asthma symptoms that do not improve with ICSs is nearly always present before the onset of eosinophilic granulomatosis with polyangiitis, a vasculitis.[20] Systemic corticosteroids are frequently needed for the treatment of eosinophilic granulomatosis with polyangiitis, either with or without further immunosuppression. Before their asthma symptoms get better, patients with these illnesses frequently need to take additional nonasthma drugs or, in the case of NSAID-exacerbated respiratory disease (also known as aspirin-exacerbated respiratory disease), desensitization with high-dose daily aspirin.[21] It has been demonstrated that leukotriene receptor antagonists alleviate symptoms in a significant proportion of individuals with exercise-induced bronchoconstriction, which may possibly be a factor in severe and enduring asthma symptoms.[22] For patients who do not respond quickly to traditional asthma medications, it is critical to accurately diagnose asthma and identify co-occurring illnesses. We advise doctors to refer patients to an asthma specialist with competence in managing persistent and refractory asthma in all cases, but especially in those when these procedures are ineffective.When treating refractory or severe symptoms, any coexisting illnesses should be addressed.

2. PATHOGENESIS

The primary cause of asthma is inflammation of the airways. Hyperresponsiveness and airflow restriction are the outcomes of this inflammation. This eventually results in thicker airway walls due to hyperplasia of the smooth muscle in the airways, thickening of the basement membrane's lamina reticularis layer, increased extracellular matrix deposition, and an increase in submucosal glands.[23]

Even with this newfound knowledge of the pathophysiology, asthma is still a complicated illness with a number of recognized subtypes. Asthma "phenotypes" are "clinically observable characteristics" of an illness that can include asthma presentation, triggers, and response to treatment. Although they don't directly correspond with the aetiology and pathophysiology of a disease, phenotypes are helpful in characterizing the clinically important aspects of an illness. Furthermore, the absence of precise and reliable markers makes it difficult to categorize asthma into different phenotypes.[24]

The classification of asthma into "endotypes" according to the immune-inflammatory pathways involved represents a significant advancement in our knowledge of the pathophysiology of asthma. Better diagnosis, patient monitoring, patient stratification, and treatment choice evaluation are made possible by this endotype-driven approach, especially in cases of severe asthma.For severe asthma, type 2 high (T2), type 2 low (non-T2), and mixed endotypes are described. There are also descriptions of a number of common pathologic pathways, including genetic, epigenetic, metabolic, and remodelling subtypes. By using biomarkers from afflicted tissues or bodily fluids, endotyping asthma offers the ability to individualize treatment for individuals and connect the primary pathogenic mechanism to a clinical asthma phenotype. [24]

Patients with asthma can find successful targeted treatment options that dramatically enhance their health by utilizing both phenotypes and endotypes. Since biologic medicines have been developed and are now widely used to treat severe asthma, this has become even more crucial.[25]

3. TRADITIONAL TREATMENT OPTIONS

Oral drugs, bronchodilators, and inhaled corticosteroids are common asthma therapies. Although there may be adverse effects from these therapies, they can help control symptoms and lower the chance of asthma episodes.

3.1 Natural Products as Alternative for Asthma Treatment

According to numerous reports from ethnopharmacological studies, the use of natural products for the treatment of physiologic disorders especially when combined with other medications is a valuable scientific tool for bioprospection exploration and the identification of novel bioactive compounds derived from natural sources.[26] Drugs derived from natural sources continue to play a major role in the discovery and development of new medications, even in the face of significant scientific advancements in chemical and pharmaceutical technologies for the synthesis of novel molecules. Originally, the foundation of these research is the conventional application of natural goods, which attracts the interest of pharmaceutical firms because of their low cost and ease of use. This enables the companies to conduct numerous studies that assess the toxicity, safety, and therapeutic actions of these items.[27-28]

Moreover, employing natural goods as adjunctive therapy is a noteworthy choice for the treatment of certain ailments. In the US, the use of natural products, vitamins, and other dietary supplements as supplementary treatments accounts for about 40% of traditional therapy. Two of the most prevalent conditions that natural products are used to treat are allergies and inflammation. The literature that is currently accessible relates alternative medicine's use of these products to immunomodulatory biochemical systems, which may help treat a variety of illnesses.[29-31]

For more than 5000 years, traditional medicine has documented the use of plant-based medicines for the treatment of asthma, ever since the Chinese utilized ephedra sinica infusions as an immune system stimulant that might minimize asthma episodes. More recently, a study by Costa and colleagues described the main natural sources of asthma treatment utilized by Brazilian families in the country's Northeast. Among the various natural components used in the study to treat children's asthma were beet, honey, onion, lemon, garlic, yarrow, mint, and honey. Asthma treatment has also made considerable reference to other naturally occurring substances, such as natural oils that can be derived from plants and animals in a variety of ways.[32]

The main natural products used in supplemental asthma therapy are oils produced from plants, as they include significant bioactive chemicals including phenylpropanoids and mono- and sesquiterpenes, which have anesthetic, antifungal, antibacterial, and anti-inflammatory properties. Additionally, animal-based oils have been used. They contain compounds from animal fluids and organs that regulate tissue oxidative capacity and have immune-modulatory effects, in addition to a variety of different saturated, mono, and polyunsaturated fatty acids. The oils derived from plants and animals are said to be effective because of the bioactive compounds included in them, which can inhibit COX-2 and COX-5. Additionally, these compounds can alter immune cell function by reducing cytokine levels of IL-4, IL-5, and IL-13; decreasing NK cell proliferation and activity and raising endogenous corticosteroid levels; assisting in the regulation of the NF-κB pathway; and reducing mucus production and inflammation of lung tissue. [33]

In this regard, Table 1 presents all of the products that were found during the investigation and included in this study, after the inclusion criteria have been examined. Because there is such a wide variety of items made from plants, only those that have three or more citations were given a thorough description in this review. However, because there aren't many studies in the scientific literature about the antiasthmatic properties of natural chemicals derived from animal and microbial sources, all of the research that satisfied the inclusion criteria is described in detail in the sections that follow. [(34-36)]

3.2 Natural Products from Plants.

There have been historical reports of centuries-old traditional medicine using natural plant-based products, particularly in China, Japan, and India. The subjects that follow deal with these goods or bioactive substances that come from the best researched plants and are used to treat asthma.

Flavonoids.

Flavonoids are naturally occurring substances found in fruits, nuts, and plants. They are classified as secondary metabolites of polyphenols and are made up of over 8,000 distinct compounds. Their chemical characteristics are attributed to the presence of two benzene rings, A and B, connected by a heterocyclic pyrene ring. They can be categorized as flavans, flavanones, isoflavanones, flavones, isoflavones, anthocyanidins, and flavonolignans based on their chemical makeup. Isoflavans, also known as flavans, have a chromane heterocyclic hydrocarbon skeleton with a phenyl group (B ring) substituted on the C ring on carbons 2 or 3. Position 4 of flavanones and isoflavanones displays an oxo-group. Flavones and isoflavones are indicated by the presence of a double bond between C2 and C3, whereas anthocyanidins are indicated by the addition of a double bond from C1 to C2. Their wide range of physiological and biological activities are attributed to the diversity of their chemical structures; among them are the anti-inflammatory, anti-allergic, antiviral, hepatoprotective, antithrombotic, and anticarcinogenic properties that stand out. According to studies included in this review, flavonoids are a class of chemicals that can be utilized to treat asthma. The primary flavonoids with antiasthmatic action that have been documented in the literature and utilized in traditional medicine are listed in the subsections that follow. These chemicals' presence in the phytocomplex is partially responsible for the antiasthmatic effect of plant extracts containing them, according to research. Chrysin, Baicalin, Luteolin, and Oroxylin A are examples of flavone compounds. Chrysin is a flavone that is defined as 5,7-dihydroxy-2-phenyl-1-4Hchromen-4-one. It is present in propolis and other plants, as well as in the blooms of Passiflora caerulea and Passiflora incarnate, as well as Matricaria chamomilla, or chamomile.Chrysin is a substance that can inhibit the

growth of smooth muscle cells in the airways and encourage a decrease in IL-4, IL-13, IgE, and interferon-γ levels, which can lessen the inflammatory response associated with asthma. In order to explain how chrysin could enhance the inhibitory effect on proinflammatory cytokines, Bae et al. conducted their research using an in vitro cell culture model. proposed that since calcium is involved in the transcription of genes that produce proinflammatory cytokines, the impact was brought about by the lowering of intracellular calcium in mast cells. Furthermore, in mice sensitized to ovalbumin (OVA), Yao and colleagues examined the protective effect of chrysin against asthma. The findings suggested that chrysin would be a promising substance with the potential to be employed in the management of asthmatic symptoms and airway remodeling. A naturally occurring metabolite, baicalin is a 7-glucuronic acid-5,6-dihydroxyflavone that is easily discovered in the leaves and bark of many Scutellaria species. Using an animal model of asthma, Park et al.'s studies examined the anti-inflammatory properties of baicalin. The findings demonstrated that this substance reduced the amounts of TNF-α and inflammatory cell infiltration in the bronchoalveolar lavage fluids (BALF). Baicalin's efficacy was ascribed to its ability to specifically inhibit PDE4 enzyme activity and reduce TNF-α production on macrophages caused by lipopolysaccharides, suggesting that this metabolite may have applications in the treatment of asthma. Apart from that, luteolin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-chromenone), another chemical with antiasthma activity, is commonly found in broccoli, green pepper, parsley, thyme, and salvia tomentosa, among other aromatic flowering plants. Shen and associates investigated its pharmacological action by blocking the GABAergic system, which is in charge of overstimulating the epithelial cells during an asthma attack, resulting in an excess of mucus formation. Research showed that by partially inhibiting GABA actions, this chemical could aid in the reduction of goblet cell hyperplasia. Oroxylin A, a flavone included in the extract of the Oroxylum indicum tree and Scutellaria baicalensis Georgi, is another antiasthmatic flavonoid component. Oroxylin A, also known as 5-7-dihydroxy-6-methoxy-2-phenylchromen-4-one, has been shown by Zhou to be able to lower BALF levels of OVA-specific IgE as well as IL-4, IL-5, and IL-13 in addition to reducing airway hyperactivity in an OVA-induced asthma mouse model. The efficacy of oroxylin A to prevent inflammatory cell infiltration in the perivascular and peribronchial zones, as determined by histological assessment, was also demonstrated in this investigation.[37-41]

Flavonol Compounds:

Kaempferol, galangin, and quercetin. As the primary active component of these plants, quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a flavonol compound that is commonly found in onions, apples, broccoli, cereals, grapes, tea, and wine. As such, it has been extensively used in traditional medicine to treat inflammatory, allergic, and viral diseases. Experiments using this chemical as an antiasthma medicine in cell cultures, rats, and in vitro and in vivo models demonstrated its great capacity to decrease inflammatory processes. Based on these investigations, quercetin's anti-inflammatory action is ascribed to inhibition and reduction of lipoxygenase and PDE4 on histamine and leukotriene release, respectively. These actions lead to a reduction in the synthesis of IL-4 and the generation of proinflammatory cytokines. Furthermore, quercetin enhanced the suppression of prostaglandin release inhibition and Ca2+ influx-induced human mast cell activation, supporting the treatment alleviation of asthma symptoms and reducing the need for short-acting β-agonists. The pharmacological action of galangin, which is chemically characterized as 3,5,7-trihydroxy-2-phenylchromen-4-one and is readily found on Alpinia officinarum, was assessed using a model of mice devoid of specific pathogens. Liu's work demonstrated both a reduction in the levels of ROS in vitro and an effective reaction to OVA-induced inflammation in vivo. Galangina additionally functioned as an antiremodeling agent in asthma, as this substance prevented the hyperplasia of goblet cells, reducing TGF-β1 levels and inhibiting the expression of VEGF and matrix metalloproteinase-9 (MMP-9) in lung tissue or BALF.The outcome demonstrated its antiremodeling ability in the TGF-β1-ROSMAPK pathway, indicating its possible application in the management of asthma. Another flavonoid, kaempferol, is mostly present in citrus fruits, broccoli, apples, and other plant sources. Its chemical definition is 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one. Because of its pharmacological potential, this molecule has been researched, particularly in relation to 24 Evidence-Based Complementary and Alternative Medicine inflammation. The OVA-induced airway inflammation mouse model of asthma used in the Chung et al. study showed that kaempferol can significantly reduce the inflammatory process by reducing inflammatory cell infiltration, inflammatory cytokine production, and IgE antibody production. Furthermore, this substance demonstrated the ability to decrease the generation of ROS within cells during the airway inflammatory response. Additionally, Mahat et al. showed that kaempferol's anti-inflammatory action is mediated by blocking nitric oxide and nitric oxide-induced COX-2 enzyme activation. This further blocks nitric oxide's cytotoxic effects and lowers the synthesis of prostaglandin-E2. In addition to describing the antiasthma action of kaempferol-3-O-rhamnoside, a glycosylated derivative of kaempferol, the previously stated work by Chung also addresses the prospect of using kaempferol as a bioactive for the development of novel treatments or medicines. In addition to lowering its toxicity, this glycosylation of kaempferol increased its solubility and stability and allowed for the synthesis of a molecule that has significant promise to expand the treatment toolbox for asthma. This reasoning suggests that the component in question may be the cause of the anti-inflammatory qualities of plant extracts that have been used to treat asthma. [42-44]

Resveratrol.

Natural stilbenoid chemical resveratrol is derived from the bark of red fruits and is a polyphenol with recognized antioxidant, promising anti-inflammatory, and anti-asthma properties. Hu et al. used eosinophils from asthmatic patients to conduct studies in which they showed that resveratrol causes both apoptosis and cell cycle arrest in the G1/S phase. This allows for a decrease in the number of eosinophils, which in turn reduces neutrophil migration and, as a result, prevents the release of histamine and PGD-2, preventing vasodilatation, mucus production, and bronchoconstriction. Furthermore, Lee et al. showed that resveratrol was efficacious against the asthmatic mouse model after this polyphenol produced a noteworthy reduction in the plasma concentration of T-helper-2-type cytokines, namely IL-4 and IL-5. Additionally, it reduced mucus hypersecretion, eosinophilia, and airway hyperresponsiveness. Despite using various methodologies, research on the scientific evidence supporting the oral administration of resveratrol as a potent natural remedy for asthmatic patients is consistent. [45-46]

Boswellia.

The Boswellia tree genus yields the oil known as frankincense, which is extracted by making cuts in the tree trunks. Polysaccharides, 5–10% essential oils, and 30–60% resin make up this oil. Research conducted on this product assessed its pharmacological properties and found that the Boswellia bioactives are boswellic acids and AKBA (3-O-acetyl-11-keto-β-boswellic acid), which both inhibit the release of IFN-gamma and IL-1, IL-2, IL-4, and IL-6 by preventing NF-κB activation. Moreover, block LOX-5 to stop leukotriene release. It is feasible to deduce that these substances, if these mediators and enzymes are engaged in the inflammation associated with asthma, may function as antiasthma molecules from the tree genus based on the physiopathology of asthma. Furthermore, a study conducted to assess the antiasthma activity of these substances revealed a significant impact on the management of bronchial asthma attributed to the combination of Boswellia serrata, Curcuma longa, and Glycyrrhiza, indicating promise for use in asthma therapy.[47]

3.3 Natural Products from Animal Source.

Natural materials produced from animals still make up a small portion of the natural sources used in asthma treatment solutions. However, a number of studies discuss the use of animal-based products as a supplemental therapy for a variety of illnesses, including asthma. These items include oils, milk, and spleen. When animal goods and parts are high in substances like lipids, prostaglandins, unsaturated fatty acids, enzymes, and polysaccharides—which are in charge of their pharmacological properties—traditional medicine trumpets the advantages of eating certain animal parts and products. The animal products and compounds cited in this session can be obtained from a variety of sources, such as mammals, amphibians, and crustaceans, demonstrating its wide range of possibilities. Additionally, animal sources are also widely cited as biocompatible and biodegradable sources, suggesting their safe use. [48-49]

Animal Sea Source:

Penaeus, Sarcophyton ehrenbergi, and Holothuroidea. Because they are home to a diverse range of animals and plants, including rare species, marine habitats are an important source of natural chemicals. Consequently, a great deal of research has been done to assess the potential antibacterial, anti-inflammatory, antiviral, and antiasthmatic properties of algae and marine life. Regarding this, Asian and Middle Eastern communities have used sea cucumbers, which are marine invertebrate animals belonging to the class Holothuroidea and are typically found in deep seas and benthic areas, in traditional medicine as an elixir because of their pharmacological activity in treating rheumatism, hypertension, cuts, burns, and constipation. The inclusion of peptides, polysaccharides, cerebrosides, and saponins in its composition is thought to be responsible for these pharmacological actions. As part of a review of the literature, Bordbar et al. cited an experimental study by Herencia et al. that demonstrated that sea cucumber extract was a powerful natural product that could be used to treat a variety of inflammatory diseases by reducing the enzymatic activity of cyclooxygenase in inflammatory mouse tissues without encouraging any modification to the cyclooxygenase enzyme. The primary component of the shrimp (Penaeus) exoskeleton, chitin, is a polysaccharide that is created by repeating units of N-acetylglucosamine to build long chain Evidence-Based Complementary and Alternative Medicine 25 through β-(1-4) linking. Ozdemir and colleagues studied the pharmacological activity of chitin. In addition to reducing airway hypersensitivity, the authors of this work administered chitin microparticles intranasally to mice in an asthma-induced mouse model, which helped to lower serum IgE and peripheral blood eosinophilia. Furthermore, five of the ten new prostaglandin derivatives that were identified and isolated from the extract of the Red Sea soft coral species Sarcophyton ehrenbergi demonstrated inhibitory activity against PDE4 (44.3%) at 10 μg.mL–1, indicating that it could be used to treat asthma and chronic obstructive pulmonary disease once PDE4 is eliminated. Ultimately, these investigations showed that since a wide range of bioproducts and/or bioactives with potential anti-inflammatory activity and antiasthmatic proprieties may be found in this environment, marine sources need to be further studied. [50]

Bullfrog (Rana catesbeiana Shaw) Oil.

The amphibian Rana catesbeiana Shaw, which is native to North America and whose meat is extensively sold worldwide, is the source of the natural oil known as bullfrog oil. Traditional medicine has utilized this oil to treat inflammatory conditions, including asthma. The medicinal benefits of this oil are attributed to a combination of bile-derived steroid component (ethyl iso-allocholate) and mono-and polyunsaturated fatty acids. Oleic, linolenic, stearic, palmitic, and myristic fatty acids can encourage the inhibition of immune cell activity, claims Yaqoob. On the basis of such data, it is conceivable to conclude that the chemical makeup of bullfrog oil makes it suitable for the treatment of conditions like asthma that are linked to inflammation. To validate this theory, more research is necessary. [51-52]

Other Products Derived from Animals.

While animal tissues make up the majority of the animal products currently used in traditional medicine to treat asthma, there is evidence that animal fluids, such as milk, colostrum, and buffalo spleen liquid, can act on the immune system to reduce asthma symptoms. In a research conducted by Neamati and associates, pigs were made asthmatic-sensitized with ovalbumin, and then the adjuvant based on the buffalo spleen fluids was given to them. When compared to healthy animals, sensitized mice showed a decrease in both the tracheal response and the quantity of white blood cells in lung lavage, indicating the fluid's ability to support asthma control. Additionally, using milk and colostrums as a natural product, which contain linolenic acid and proteins such lactoferrin, another study was conducted to assess the antiasthma activity. This study demonstrated that ragweed pollen grain extract reduced allergic airway inflammation and altered the content of plasma lipids in both human and animal models. [53]

Bioactives Obtained from Microorganisms.

Since the discovery of penicillin, there has been extensive reporting on the use of metabolites from bacteria and fungus to treat a variety of illnesses. More recent research has, however, looked into these metabolites' potential for antiasthma treatment. Regarding this issue, a study conducted by Lu and associates assessed the antiasthma efficaciousness of the bacterial lysate OM85 Broncho-Vaxom (BV), a proprietary pharmaceutical item. According to the study, the bacterial lysate and traditional therapy together were able to raise the number of natural killer T cells in peripheral blood, which in turn reduced the level of cytokines (the kind of which was not specified) and helped to lessen asthma symptoms. Additionally, the in vivo anti-inflammatory effect of kefir, a fermented milk beverage made from bacteria that create lactic and acetic acids, was assessed. Kefiran is an insoluble polysaccharide that is the primary ingredient in kefir. This chemical was able to decrease INF-c and TNF-α production as well as the release of IL-4, IL-6, and IL-10 to normal levels. Furthermore, kefiran administered intragastrically aided in the reduction of OVA-induced cytokine production in a mouse asthma model, hence reducing mucus hypersecretion and pulmonary eosinophilia. Therefore, it is vital to emphasize that these new agents may contribute to the existing treatment of asthma based on these studies and historical facts surrounding the use of microbes as source for the separation of new bioactives and the development of medicines.[54-55]

4. BIOLOGIC THERAPIES

A more recent kind of asthma medication called biologic treatments targets particular molecules involved in the inflammatory process. Patients with severe asthma who do not respond to conventional therapy have seen improvement with these treatments.

there are five biologics approved in South Korea as treatment for SA, all of which are drugs for T2-high asthma. The characteristics of these biologics are summarized in Tables 1 and and 2.

Table 1. Summary of the biologics currently approved for severe asthma in Korea

Biologics (trade name)	Mechanism of action	Indication	Dose and route
Mepolizumab (Nucala)	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	≥18 yr old; AEC ≥150 cells/μL or ≥300 cells/μL at least once a year	00 mg SC every 4 wk
Reslizumab (Cinqair)	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	≥18 yr old; AEC ≥400 cells/μL	Weight-based dosing of 3 mg/kg IV every 4 wk
Omalizumab (Xolair)	Anti-IgE; prevents IgE from binding to its receptor on mast cells and basophils	≥6 yr old; positive allergy testing (allergic asthma); IgE, 30–700 IU/mL	0.016 mg/kg per IU of IgE SC every 2–4 wk
Dupilumab (Dupixent)	Anti–IL-4R; binds to IL-4 receptor α; blocks signaling of IL-4 and IL-13	≥12 yr old; AEC ≥150 cells/μL or FeNO ≥25 ppb with OCS-dependent	400–600 mg SC loading dose followed by 200 or 300 mg SC every 2 wk
Biologics (trade name)	**Asthma exacerbation**	**Lung function improvement**	**Corticosteroid weaning**
Omalizumab (Xolair)	Reduces by 25%–50%	Minimal or equivocal improvement	Decreases use of ICS, but no clear data that it facilitates with OCS weaning
Reslizumab (Cinqair)	Reduces by 50%–60%	Improved	OCS weaning has not been evaluated for this indication
Mepolizumab (Nucala)	Reduces by 50%	Some, but not all, studies showed some improvement	Decreases total use of OCS
Benralizumab (Fasenra)	Reduces by 25%–60%	Improved	Decreases total use of OCS Facilitate discontinuation of chronic OCS (50%)
Dupilumab (Dupixent)	Reduces by 50%–70%	Improved	Decreases total use of OCS Facilitate discontinuation of chronic OCS (50%)

5. PERSONALIZED MEDICINE

Treatments for asthma that are tailored to each patient have been made possible by advances in genetic research. Doctors can more effectively and safely customize medicines for each patient by detecting unique genetic markers.

The goal of the precision medicine approach is to identify predictive factors that will enable a more precise determination of the best course of action for a given disease in a given patient population. Precision medicine, thus, is the antithesis of the so-called "one-size-fits-all" approach, which applies therapeutical techniques and clinical judgments without taking the potential person into account. The ability to categorize people into subpopulations that vary in their susceptibility to a specific disease is implied by precision medicine. "Choosing wisely" and "slow medicine," whose goals are the best for the patient while controlling sustainability of the process, are two more methods that are highly relevant in this context. The precision-medicine approach uses surrogate measurements that function as biomarkers to investigate the underlying causes of various kinds of each disease (called "endotypes") in order to identify subpopulations of patients, or "phenotypes". The availability of readily assessable biomarkers—possibly with point-of-care technology—as well as the body of knowledge necessary to accurately translate biomarker results into a personalized clinical–therapeutical decision are prerequisites for providing precision medicine to patients in routine clinical settings. Consequently, we should be aware that a few well-equipped reference centers with highly qualified staff will oversee a customized and exact strategy, such as in the case of severe asthma. When US President Barack Obama announced in 2015 that he intended to fund a "Precision Medicine Initiative" with the goal of "enabling a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments," physicians and researchers began to prioritize the precision-medicine approach. The National Institutes of Health's research spending in the upcoming ten years has validated this effort early this year. Two novel biologics, mepolizumab (a monoclonal antibody against IL-5) and reslizumab (an additional anti-IL monoclonal antibody), have been licensed for severe asthma after the first biologic agent, umalizumab, was developed ten years ago. We are now at the beginning of a new era in the management of patients with severe asthma: the "Precision Medicine Era." In the coming years, more will be introduced, such as benralizumab, an IL-5 receptor antagonist; dupilumab, an IL-4 receptor alpha antagonist that blocks both the IL-4 and IL13 inflammatory pathways; and tezepelumab, an antithymic stromal lymphopoietin (TSLP) antibody. In actuality, in order to tailor the therapeutic strategy, people with severe asthma must be clinically, functionally, inflammatoryally, and molecularly phenotyped. [57-60]

5.1 Telemedicine

Through virtual consultations, telemedicine enables patients to obtain distant medical care, including control of their asthma. Patients who reside in rural or underserved locations may find this to be especially helpful. Practitioners have utilized telemedicine to address concerns with access to care and to supplement medical care prior to the COVID-19 epidemic. Nonetheless, there have been significant adjustments to the healthcare system, requiring virtual visits or, in certain situations, the adoption of a hybrid approach. During this time, telemedicine was employed by patients and physicians to treat asthma patients out of need and frequently as the only available option. To ensure the patient's and the provider's health and welfare, visits were conducted remotely. Currently, private practitioners and healthcare systems are developing a post-pandemic contingency plan that may include telemedicine options as standard of treatment.Depending on the purpose behind its utilization, telemedicine can be carried out in a variety of methods. Direct-to-consumer (DTC) and facilitated virtual visits are two types of live or synchronous TM visits used for asthma care (FVVs). A visit can be conducted asynchronously if it is not required to occur in real time. These consist of e-consults, mobile health (mHealth) apps, and remote patient monitoring (RPM). The kind of telemedicine platform that is employed should depend on the objective the physician is attempting to accomplish with asthma care, as was stated in a recent editorial. Consequently, mHealth, DTC, FVVs, RPM, communication through patient portals, and e-consult usage.[62]

5.2 Smart Inhalers

Smart inhalers are inhalers that measure drug usage and give patients feedback through the use of sensors. By doing this, patients can make sure they are taking their medication as prescribed and control their asthma more effectively. Over 200 million people worldwide suffer with OPD, and an additional 300 million from asthma. The burden of chronic diseases worldwide is made up of little over 8% chronic respiratory diseases.Patients must follow a tight medication schedule, adjusting the dosage and time as needed to achieve symptom control, in order to lessen the clinical severity of these illnesses. Since they eliminate the need for injectables and the side effects of oral medications, inhalers are crucial for adhering to the stringent schedule needed for these disorders.However, a lot of patients abuse the independence that comes with using inhalers by not following the prescribed treatment plan, forgetting to stock up on refills before the last one runs out.

5.3 Environmental Interventions

Air filters and bedding free of allergens are two examples of environmental interventions that might help lessen exposure to asthma triggers. Children who have asthma may benefit most from these measures.

6. BIOMARKER-TARGETED THERAPIES

Apart from their function in characterizing phenotypes and endotypes, biomarkers might also be predictive in identifying individuals who will respond to specific biological treatments. Serum IgE and blood eosinophils were the most researched biomarkers that may be used to select the appropriate

endotype-based treatment. Serum total IgE levels between 30 and 1500 IU/ml are really used to confirm if a patient with severe allergic asthma is a good candidate for anti-IgE therapy (omalizumab). Peripheral blood count is the biomarker selected to determine the possibility of prescribing anticytokine methods (e.g., anti-IL5, anti-IL4/IL-13,...) that are currently accessible or closely available. For the purpose of prescribing biologicals for the eosinophilic refractory forms of severe asthma, a number of cutoffs in blood eosinophil measurements were selected. These range from 150/ml for dupilumab (newer data did not confirm eosinophils as a predictive biomarker of response to dupilumab) and mepolizumab (with at least one historical report of more than 300/ml for the latter), to 300/ml for benralizumab and 400/ml for reslizumab trials. When looking for predictive biomarkers of biological treatment response, a proteomic method revealed a direct correlation between galectin-3 tissue levels and a favorable response to omalizumab in terms of decreased airway remodeling. Patients with high serum periostin levels responded best to lebrikizumab, an anti-IL13 medication, in terms of improved lung function, according to post hoc analysis of clinical studies. Additionally, as previously discussed about POCT, improvements in terms of a decrease in exacerbations in individuals receiving omalizumab are positively correlated with high FENO, high-serum periostin, and high-blood eosinophil levels.[61]

7. COCLUSION

For many years, doctors have understood that the cause of severe and chronic asthma is heterogeneous illnesses with common symptoms. Numerous investigations conducted in more recent times have confirmed the heterogeneity across asthma endotypes and phenotypes. New classes of asthma medications that target specific immunological pathways have been developed and tested as a result of these results, particularly the identification of unique immune phenotypes. Physicians can now provide patients with severe asthma tailored treatment thanks to emerging technologies. Because asthma is a complicated illness, the best course of treatment necessitates both a step-by-step titration of medicine based on the unique symptoms and immune pathway drivers of each patient. With the aid of biomarkers, asthma can now be phenotyped and endotyped. Additionally, biologic medicines that target particular immune pathways can be developed, which has resulted in substantial advancements in the control of severe disease and holds great promise for future therapeutics. In a world that is changing quickly, a more individualized approach to asthma therapy has revolutionized the industry and brought about significant modifications to suggested management in recent years. Only omalizumab has been accessible over the past ten years; mepolizumab and, presumably, the other monoclonal antibodies that were previously mentioned will follow. When there is no longer just one monoclonal antibody available, we will have to select one monoclonal antibody from a range of options. This means that more precise and personalized medicine will be required to identify the appropriate biological marker for every patient, which will require the use of panels or more selective biomarkers.

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