Plant-Derived Natural Products against Common Respiratory Diseases

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Currently, the world is more challenged by respiratory diseases (RDs) than it witnessed in the last few decades. This is evident in the plethora of acute and chronic respiratory conditions, ranging from asthma and chronic obstructive pulmonary disease (COPD) to multidrug-resistant tuberculosis, pneumonia, influenza, and more recently, the novel coronavirus (COVID-19) disease. Unfortunately, the emergence of drug-resistant strains of pathogens, drug toxicity and side effects are drawbacks to effective chemotherapeutic management of RDs. The role of natural products (NPs) in drug discovery cannot be over-emphasized. NPs are chemical substances produced by living organisms such as plants, animals, and marine organisms. They are primary and secondary metabolites and may only be isolatable in small quantities from natural sources. Structurally, they range from small molecules, such as thymol, thymoquinone and penicillin, to complex molecules such as tachyplesin I and II, with unique chemical and biological properties. NPs are regarded as the hallmark of modern pharmaceutical care because they continue to provide new leads with novel biological mechanisms of action against emerging diseases.

respiratory diseases natural products plant-derived compounds

1. Introduction

The human respiratory system, otherwise known as the ventilatory system, is a biological system made up of specific organs and structures such as oropharyngeal and nasopharyngeal cavities, larynx, and trachea (upper respiratory tract), and the lower respiratory tract, which includes bronchi, lungs, and diaphragm [1][2][3]. The lungs are an important part of the respiratory system that facilitate gas exchange from the environment into the bloodstream for healthy living [4].

The respiratory functions can be hampered by infections and diseases of the lungs and their associated organs and structures. These diseases are categorised as obstructive and restrictive lung diseases [4]. Examples of obstructive lung diseases are asthma and chronic obstructive pulmonary disorder (chronic bronchitis), while restrictive lung diseases include idiopathic pulmonary fibrosis, pneumoconiosis, and sarcoidosis [5]. These respiratory diseases (RDs), otherwise referred to as “respiratory disorders”, “airways diseases”, “pulmonary diseases” or lung diseases, often arise from bacterial and viral infections in the upper and lower respiratory tracts, causing the common cold, otitis, sinusitis, pharyngitis, epiglottitis, laryngotracheitis, bronchitis, bronchiolitis, and pneumonia [6]. Some of the causative agents include *Mycobacterium tuberculosis*, *Haemophilus influenza* type b., *Streptococcus pyogenes*, *Chlamydia* sp., and *Candida albicans* [7].

Some viral infections of the respiratory tracts are implicated in disease pandemics such as influenza (flu), Middle east respiratory syndrome coronavirus (MERS-CoV), and more recently, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-causing COVID-19 disease that is currently ravaging the world [8]. SARS-CoV and MERS-CoV broke out in 2003 and 2012, respectively [9], and influenza claimed about 389,000 lives globally in the year 2017 [10]. As of 22 January 2022, about 5.59 million people had died from 346 million reported cases of COVID-19 globally [11]. These show the significant negative impacts of RDs on individual lives, national development, and human existence.

2. Plant-Derived Natural Products as Lead Agents against Common Respiratory Diseases

Natural products (NPs) are generally described as chemical substances produced by living organisms that are found in nature [12]. Natural product sources include plants, animals, lower and marine organisms, and minerals [13]. Plant-derived NPs are characterised by enormous chemical entities with structural complexities, which are optimized by evolution to serve specific biological functions [14]. These structurally diverse substances, also referred to as metabolites, especially secondary metabolites, produce physiological actions in man; thus, offering great therapeutic value [15].

Historically, they continue to play a key role in the therapeutic armoury of mankind against diseases. The earliest records of NPs were plant extracts such as oils from Cypress (*Cupressus sempervirens*) and *Myrrh* (*Commiphora* species), inscribed on clay tablets in cuneiforms from Mesopotamia (2600 B.C.), which are still used today ethnomedicinally to treat colds, coughs, and inflammation [15]. The Egyptian pharmaceutical record (Ebers Papyrus, 2900 B.C.) documented over 700 plant-based drugs in the forms of gargles, infusions, ointments and pills [16]. The Chinese Materia Medica contained 52 prescriptions, the Shennong Herbal (~100 B.C.) enlisted 365 drugs, while the Tang Herbal (659 A.D.) contained 850 drugs, and all were documented records on the medicinal uses of NPs [16]. The Greek physician Dioscorides (100 A.D.) recorded the collection, storage and uses of medicinal herbs. Monasteries in England, Ireland, France and Germany preserved the Western knowledge of natural medicines during the Dark and Middle Ages, whilst the Arabs preserved the Greco-Roman knowledge and expanded the uses of their own resources, together with Chinese and Indian herbs [16]. Avicenna, a Persian pharmacist, physician, philosopher and poet, contributed much to the science of pharmacy and medicine in the 8th century through his work titled “Canon Medicinae” [16].

The early years of the 20th century witnessed remarkable drug discoveries from natural sources. The world’s first broadly effective antibiotic substance, penicillin, was first isolated from the fungus *Penicillium notatum* by Sir Alexander Fleming, a Scottish physician and microbiologist, in 1928 [17]. This discovery led to the re-isolation and in vivo and clinical studies by Fleming and co-workers in the early 1940s and commercialization of synthetic penicillins, which ultimately revolutionized drug discovery and won them the 1945 Nobel Prize in Physiology and Medicine [18]. After the first clinical report on penicillin G, there was global interest in exploiting many natural resources for new bioactive natural products. The post-Fleming era witnessed the isolation of some sulphur-containing secondary metabolites (natural antibiotics) such as aztreonam, nocardicin G and imipenem from marine

organisms [15]. Erythromycin was discovered from *Saccharopolyspora erythraea* as an antibacterial drug with a 14-membered macrocycle composed entirely of propionate units, broadly active against Gram-positive cocci and bacilli, and is used for mild to moderate upper and lower respiratory tract infections [19].

Plant-derived NPs continue to contribute significantly to the discovery of newer drugs. For example, the bark of Pacific yew plant, *Taxus brevifolia*, gave taxol, a cytotoxic compound that was latter developed as Paclitaxel for the treatment of human lung cancer and other malignant tumours [20]. Some antiviral flavonoids such as 6-hydroxyluteolin 7-*O*-β-d-glucoside, nepitrin and homoplantaginin were isolated from the methanol extract of *Salvia plebeia*. These compounds were found to be active against influenza virus H1N1A/PR/9/34 neuraminidase [21]. Matteflavoside G from the rhizomes of *Onoclea struthiopteris* showed significant inhibitory activity against the H1N1 influenza virus neuraminidase with an EC_{50} value of 6.8 ± 1.1 μM and an SI value of 34.4 [22]. Extracts of *Humulus lupulus* and five South African medicinal plants, namely *Volkameria glabra*, *Cussonia spicata*, *Myrsine melanophloeos*, *Pittosporum viridiflorum* and *Tabernaemontana ventricose*, are known in traditional medicine to manage inflammatory and respiratory diseases such as the influenza virus, with quercetin and rutin identified among their putative active constituents [23].

A study of high-throughput screening (HTS) by Novartis revealed that NPs were the most diverse compounds tested, with significantly higher hit rates compared to the compounds sourced from the synthetic and combinatorial libraries [24]. Some potential natural anti-TB agents include the antifungal phenazine and riminophenazine isolated from lichens. Clofazimine is a riminophenazine and TB drug originally discovered in 1954 through structural modifications of diploicin, extracted from *Buellia canescens*. It is currently used as a WHO group-five drug for multidrug resistant tuberculosis (MDR-TB) [25]. Natural products and NP-derived compounds, such as aztreonam, colistin, and tobramycin, have been developed for cystic fibrosis as inhalation drugs, while amikacin, arbekacin, and capreomycin are being developed for nontuberculous mycobacterial infection, bacterial pneumonia, and tuberculosis, respectively [26].

For decades, many herbs and spices have been known to be used in folkloric medicines for the management of respiratory diseases. Some of these medicinal spices and herbs are now well established in modern medicine as dietary supplements, nutraceuticals, and whole drugs because of their identified and well-defined bioactive agents [27]. The peel methanol extract of *Opuntia ficus-indica,* known as the prickly pear cactus, has been reported to contain some in vitro anti-pneumonia compounds such as astragalin, quercetin 5,4′-dimethyl ether, isorhamnetin-3-O-glucoside and isorhamnetin [28]. Curcumins from the turmeric rhizomes (*Curcuma longa*) are known anti-inflammatory, antiviral, immune modulating, anti-lung cancer and anti-SARS-CoV-2 agents, as well as inhibitors of acute and chronic respiratory disorders [29][30]. Gingerols, 6-shogaol, zingerone, gingerenone-A, 6-dehydrogingerdione, β-bisabolene, α-curcumene and β-sequiphellandrene, all from the bulbs of ginger (*Zingiber officinale*), are known bioactive agents against asthma, inflammation, lung cancer, acute and chronic respiratory disorders, and respiratory viruses including coronaviruses [31]. 6-Gingerol was reported to decrease the gene expression and production of MUC5AC, through affecting the ERK- and p38 MAPK signalling pathways, thus inhibiting pro-inflammatory actions of many pulmonary diseases [32]. *Nigella sativa* L. (black cumin seeds) contain bioactive agents such as nigelline, thymol, thymoquinone, nigellidine, nigellicine, carvacrol, p-cymene, 4-terpineol,

trans-anethol, α-pinene, α-hederin, and kaempferol-3-glucoside [33]. The constituents improved antioxidant enzymes (catalase, glutathione peroxidase and glutathione-*S*-transferase), and exhibit anti-inflammatory, immune modulatory and broncho-dilatory effects against obstructive RDs [33]. The inhibitory effect of nigellone on the release of histamine from mast cells has been implicated for the management of bronchitis and asthma [34].

Additionally, some NPs such as the anti-influenza ginkgetin, 4′-*O*-methylochnaflavone, hinokiflavone from *Ginkgo biloba*; six cinnamic amide alkaloids from *Tribulus terrestris* with considerable in silico SARS-CoV PLpro activity; procyanidin B1, procyanidin A2 and cinnamtannin B1 from the dried bark (cortex) of *Cinnamomum verum* with in vitro anti-SARS-CoV activity; and resveratrol and pterostilbene from grapes (*Vitis vinifera*) interfered with the SARS-CoV-2 infection cycle and significantly inhibited COVID-19 infection in primary human bronchial epithelial cells cultured under air–liquid interface conditions [9]. Likewise, some triterpenoids such as oleanolic acid, betulinic acid, ursolic acid and saikasaponins A, C, D, B1, B2, B3, and B4, which have been isolated from some medicinal plants, are known to exhibit significant antioxidant, anti-inflammatory, cytotoxic, antibacterial, antiviral and immune modulatory activities in lung diseases such as COPD, bronchitis, lung cancer, influenza and coronaviruses [9][32][35][36][37][38].

3. Structure–Activity Relationships of Some Promising Natural Products against Common Respiratory Diseases

The study of the structure–activity relationships (SARs) is an approach designed to find the relationships between chemical structures of ligands and biological targets of studied compounds [39]. It has become increasingly essential as a tool for organizing, mining, and interpreting data, to guide further investigation for drug discovery [40]. It is also a strategy to increase the value of the activity initially detected [41]. Natural products contain steric and electronic features in their bioactive sites (pharmacophores), which are responsible for the optimal supramolecular interactions with specific biologic targets and to trigger (or block) their biologic responses. The most used features for describing pharmacophore sites are hydrogen bond acceptors and donors, acidic and basic functional groups, aliphatic and lipophilic moieties, aromatic- and hydroxyl-hydrophilic moieties amongst others [42].

Reports have shown the SARs of some natural products implicated against some common respiratory diseases. Pires et al. [43] reported the influence of methyl-, hydroxyl-, and carbonyl functional groups on the in vitro anti-TB activities of eight coumarin derivatives from *Calophyllum brasiliense*, with MIC ranging from 15.6–62.5 µg/mL and a cytotoxicity range of 4.5–82.0 µg/mL against *Mycobacterium tuberculosis* H37Rv and its multidrug-resistant clinical isolates. Here, the carbonyl and hydroxyl groups enhance anti-*M. tuberculosis* activity by the inhibition of acid-fastness formation in the mycobacterial cell wall, while the presence of lipophilic side chains such as the alkyl substituent at the C-3 position and the presence of double bonds increase the lipophilicity of the compound, thus, helping it to penetrate the lipid-enriched mycobacterial cell wall [43].

Quercetin 5,4′-dimethyl ether isolated from the fruit peel methanol extract of *Opuntia ficus-indica* has been reported to demonstrate double-fold in vitro anti-pneumonia activities, with MIC values of 0.49 and 0.98 µM against *Klebsiella pneumonia* and *Moraxella catarrhalis*, respectively, when compared to Imipenem, a standard anti-

pneumonia drug [28]. Furthermore, an in silico molecular docking study of the compound revealed high H-bonding affinity with key amino acids such as threonine, asparagine, and tyrosine, thus suggesting it to be a natural quorum-sensing inhibitor, which is a key anti-pneumonia property [31]. Wollamide B isolated from *Streptomyces nov. sp.* (MST-115088) has been reported to show considerable in vitro anti-TB activity with an IC_{50} value of 3.1 µM against *Mycobacterium bovis*. The presence of the basic amino acid ornithine and clusters of lipophilic amino acids was shown to significantly contribute the typical cationicity and amphiphilicity to the molecule [44].

The presence of *C*- and *N*-glycosylation has also been reported to enhance in vitro anti-TB activity. For instance, the *C*-glycosylated benz[α]anthraquinone derivatives and an *N*-glycosylated arenimycin isolated from *Streptomyces* species and *Salinispora arenicola*, respectively, showed strong activity against *Mycobacterium tuberculosis* within an MIC range of 5.88–24.32 µM, while the latter molecule exhibited an MIC value of 1.5 µM [45]. It is also noteworthy that unsaturation in the C ring (Δ^2), the number and position of hydroxyl groups at the A and B rings, and the carbonyl group at C-4 of ring C for natural flavonoids are reported to contribute considerably to their anti-inflammatory properties in some common lung diseases [46].

4. Mechanisms of Action of Some Plant-Derived Lead Compounds against Common Respiratory Diseases

Often, the human respiratory tracts become liable to inflammation upon microbial (especially bacterial and viral) infection and physical injury [47]. Respiratory inflammation is a hallmark of many respiratory diseases, which include asthma, COPD, and acute respiratory disorders (ARDs) [48]. During the inflammation process, inflammatory cells, which include eosinophils, lymphocytes, and macrophages, are activated to serve as the sources of different inflammatory mediators such as histamine, interleukins (IL-4, IL-1β, IL-6, and IL-5), leukotriene, prostaglandins, nitric oxide, and tumour necrosis factor (TNF-α) [49]. The release of these inflammatory mediators causes several abnormalities in the lungs and their function [48][49]. Therefore, natural products (NPs) that can target the epithelial–mesenchymal transition (EMT), oxidative stress, fibroblast activation, inflammatory injury, metabolic regulation, and extracellular matrix accumulation within the respiratory tracts are regarded as candidate anti-inflammatory agents that can be optimized as leads for new respiratory drugs [50]. The basic mechanism of action of the chemical agents involves regulating redox status, inhibiting the activities of bacteria and viruses, regulating the protease/anti-protease balance, blocking the NF-κB and MAPK signalling pathways, inhibiting the production of cytokines, suppressing the activation and migration of inflammatory cells, inhibiting the synthesis and activation of adhesion factors and growth factors, controlling the cAMP-PKA and PI3K/Akt signalling pathways, and increasing TIMP-1 expression to serve as anti-inflammatory agents in the lungs [49][51].

The anti-inflammatory properties of curcumins against lung inflammation induced *Klebsiella pneumonia* has been demonstrated in a mouse model experiment [52]. Here, it was shown that curcumin ameliorates lung inflammation considerably by decreasing the bacterial load in the lung tissue and inducing a significant decrease in neutrophil influx into the lungs as well as in the production of MDA, NO, and MPO activity and TNF-alpha levels, whereas Augmentin, the standard antibiotic, takes care of bacterial proliferation. The study, however, highlighted the potential usefulness of curcumin as an adjunct therapy along with some antibiotics as an anti-inflammatory or an

immunomodulatory agent in the case of acute lung infection [52]. Studies have also shown the significant anti-inflammatory actions of quercetin, which are believed to be mediated through the inhibition of phospholipase A2 (via arachidonic acid), lipoxygenase, cyclooxygenase, and thromboxane enzymes and through the modulation of iNOS, thereby inhibiting NO production [53][54].

Some alkylated chalcones such as xanthoangelol A-G, isolated from *Angelica keiskei* leaves, have been reported to show considerable in vitro and in silico anti-SARS-CoV activity. Xanthoangelol D particularly inhibited the SARS-CoV cysteine proteases with an IC_{50} of 1.2 µM, by both competitive and non-competitive modes, thus suggesting the molecule to be a candidate protease inhibitor in SARS-CoV-related infections [55]. Similarly, some natural phenolic compounds such as brazilin, theaflavin-3,3′-digallate and curcumin have been reported to have remarkable in vitro anti-SARS-CoV-2 activity with an $IC_{50} \geq 10$ µM, among 56 polyphenolic compounds and plant extracts that were tested. The compounds were said to bind with the receptor-binding domain of SARS-CoV-2 spike protein, thus significantly inhibiting viral attachment to the human angiotensin-converting enzyme 2 receptor and cellular entry of pseudo-typed SARS-CoV-2 virions [56].

Tetragalloyl quinic acid isolated from *Galphimia glauca* has been reported as an in vivo anti-asthmatic agent at 5 mg/kg orally, by suppressing allergen- and platelet-activating factor, PAF-induced bronchial obstruction, PAF-induced bronchial hyperreactivity, and thromboxane biosynthesis in vitro. Androsin from *Picrorhiza kurroa* also demonstrated similar in vivo activity at 10 mg/kg orally (0.5 mg inhalative) by preventing allergen- and PAF-induced bronchial obstruction [57].

Additionally, ganoderic acid C1 in the ASHMI™ herbal formula comprising *Ganoderma lucidum Sophora flavescens* and *Glycyrrhiza uralensis* has been reported to have potential for treating TNF-α mediated inflammation in asthma and other inflammatory diseases [58]. Based on clinical studies, the herbal formula significantly reduced TNF-α production by murine macrophages (RAW 264.7 cells) and peripheral blood mononuclear cells (PBMCs) from asthma patients [58][59]. The inhibition was associated with down-regulation of NF-κB expression and partial suppression of MAPK and AP-1 signalling pathways [59].

The combination of synephrine and stachydrine, both alkaloids from the dried rind of ripe *Citrus reticulata* Blancon fruits, has been reported to show significant spasmolytic effects on acetylcholine chloride (ACh)-induced contractions in isolated guinea pig trachea by activating β-2 adrenergic receptor signalling [60]. They also showed synergistic protection against histamine-induced experimental asthma by prolonging the latent period. Stachydrine acts as the antitussive component and is capable of significantly reducing citric acid-induced coughing; thus, the broncho-dilatory and antitussive effects of the combined alkaloids might explain their use in traditional Chinese medicine as an anti-asthmatic remedy [60].

References

1. Campbell, N.A. 1993 Biology. 3rd Edition, Benjamin/Cummings, Francis Group, Redwood City-References-Scientific Research Publishing. Available online: https://www.scirp.org/(S(i43dyn45teexjx455qlt3d2q))/reference/ReferencesPapers.aspx?ReferenceID=1556565 (accessed on 22 January 2022).
2. Hsia, C.C.W.; Hyde, D.M.; Weibel, E.R. Lung Structure and the Intrinsic Challenges of Gas Exchange. Compr. Physiol. 2016, 6, 827.
3. El-Kased, R.F. Natural Antibacterial Remedy for Respiratory Tract Infections. Asian Pac. J. Trop. Biomed. 2016, 6, 270–274.
4. Haddad, M.; Sharma, S. Physiology, Lung. Available online: https://www.ncbi.nlm.nih.gov/books/NBK545177/ (accessed on 22 January 2022).
5. Mannino, D.M.; Ford, E.S.; Redd, S.C. Obstructive and Restrictive Lung Disease and Functional Limitation: Data from the Third National Health and Nutrition Examination. J. Intern. Med. 2003, 254, 540–547.
6. Bacterial Respiratory Tract Infection—The Lung Docs. Available online: https://www.thelungdocs.com/services/respiratory-infections/ (accessed on 22 January 2022).
7. Rosati, L.A.; Leslie, K.O. Lung Infections. Pract. Pulm. Pathol. A Diagn. Approach. 2011, 137–211.
8. Piret, J.; Boivin, G. Pandemics Throughout History. Front. Microbiol. 2021, 11, 3594.
9. Omrani, M.; Keshavarz, M.; Nejad Ebrahimi, S.; Mehrabi, M.; McGaw, L.J.; Ali Abdalla, M.; Mehrbod, P. Potential Natural Products against Respiratory Viruses: A Perspective to Develop Anti-COVID-19 Medicines. Front. Pharmacol. 2020, 11, 2115.
10. Paget, J.; Spreeuwenberg, P.; Charu, V.; Taylor, R.J.; Iuliano, A.D.; Bresee, J.; Simonsen, L.; Viboud, C. Global Mortality Associated with Seasonal Influenza Epidemics: New Burden Estimates and Predictors from the GLaMOR Project. J. Glob. Health 2019, 9, 020421.
11. WHO Coronavirus (COVID-19) Dashboard|WHO Coronavirus (COVID-19) Dashboard with Vaccination Data. Available online: https://covid19.who.int/ (accessed on 22 January 2022).
12. Sorokina, M.; Steinbeck, C. Review on Natural Products Databases: Where to Find Data in 2020. J. Cheminform. 2020, 12, 20.
13. Leisegang, K. Herbal Pharmacognosy: An Introduction. In Herbal Medicine in Andrology; Elsevier Inc.: Amsterdam, The Netherlands, 2021; pp. 17–26.
14. Atanasov, A.G.; Zotchev, S.B.; Dirsch, V.M.; Orhan, I.E.; Banach, M.; Rollinger, J.M.; Barreca, D.; Weckwerth, W.; Bauer, R.; Bayer, E.A.; et al. Natural Products in Drug Discovery: Advances and Opportunities. Nat. Rev. Drug Discov. 2021, 20, 200–216.

15. Dias, D.A.; Urban, S.; Roessner, U. A Historical Overview of Natural Products in Drug Discovery. Metabolites 2012, 2, 303–336.
16. Haefner, B. Drugs from the Deep: Marine Natural Products as Drug Candidates. Drug Discov. Today 2003, 8, 536–544.
17. Tan, S.Y.; Tatsumura, Y. Alexander Fleming (1881–1955): Discoverer of Penicillin. Singap. Med. J. 2015, 56, 366.
18. Wainwright, M. Miracle Cure: The Story of Penicillin and the Golden Age of Antibiotics. Available online: https://www.wiley.com/en-gb/Miracle+Cure%3A+The+Story+of+Penicillin+and+the+Golden+Age+of+Antibiotics-p-9780631164920 (accessed on 26 February 2022).
19. Maplestone, R.A.; Stone, M.J.; Williams, D.H. The Evolutionary Role of Secondary Metabolites—A Review. Gene 1992, 115, 151–157.
20. Success Story: Taxol. Available online: https://dtp.cancer.gov/timeline/flash/success_stories/s2_taxol.htm (accessed on 26 February 2022).
21. Bang, S.; Li, W.; Ha, T.K.Q.; Lee, C.; Oh, W.K.; Shim, S.H. Anti-Influenza Effect of the Major Flavonoids from Salvia Plebeia R.Br. via Inhibition of Influenza H1N1 Virus Neuraminidase. Nat. Prod. Res. 2018, 32, 1224–1228.
22. Li, B.; Ni, Y.; Zhu, L.J.; Wu, F.B.; Yan, F.; Zhang, X.; Yao, X.S. Flavonoids from Matteuccia Struthiopteris and Their Anti-Influenza Virus (H1N1) Activity. J. Nat. Prod. 2015, 78, 987–995.
23. Mehrbod, P.; Abdalla, M.A.; Fotouhi, F.; Heidarzadeh, M.; Aro, A.O.; Eloff, J.N.; McGaw, L.J.; Fasina, F.O. Immunomodulatory Properties of Quercetin-3-O-α-L-Rhamnopyranoside from Rapanea Melanophloeos against Influenza a Virus. BMC Complement. Altern. Med. 2018, 18, 184.
24. Sukuru, S.C.K.; Jenkins, J.L.; Beckwith, R.E.J.; Scheiber, J.; Bender, A.; Mikhailov, D.; Davies, J.W.; Glick, M. Plate-Based Diversity Selection Based on Empirical HTS Data to Enhance the Number of Hits and Their Chemical Diversity. J. Biomol. Screen. 2009, 14, 690–699.
25. Caminero, J.A.; Sotgiu, G.; Zumla, A.; Migliori, G.B. Best Drug Treatment for Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis. Lancet Infect. Dis. 2010, 10, 621–629.
26. Igarashi, M.; Ishizaki, Y.; Takahashi, Y. New Antituberculous Drugs Derived from Natural Products: Current Perspectives and Issues in Antituberculous Drug Development. J. Antibiot. 2017, 71, 15–25.
27. Mahomoodally, M.F. Traditional Medicines in Africa: An Appraisal of Ten Potent African Medicinal Plants. Evid.-Based Complement. Altern. Med. 2013, 2013, 617459.

28. Elkady, W.M.; Bishr, M.M.; Abdel-Aziz, M.M.; Salama, O.M. Identification and Isolation of Anti-Pneumonia Bioactive Compounds from Opuntia ficus-indica Fruit Waste Peels. Food Funct. 2020, 11, 5275–5283.
29. Alexandrow, M.G.; Song, L.J.; Altiok, S.; Gray, J.; Haura, E.B.; Kumar, N.B. Curcumin: A Novel Stat3 Pathway Inhibitor for Chemoprevention of Lung Cancer. Eur. J. Cancer Prev. 2012, 21, 407–412.
30. Rattis, B.A.C.; Ramos, S.G.; Celes, M.R.N. Curcumin as a Potential Treatment for COVID-19. Front. Pharmacol. 2021, 12, 1068.
31. Mao, Q.Q.; Xu, X.Y.; Cao, S.Y.; Gan, R.Y.; Corke, H.; Beta, T.; Li, H. bin Bioactive Compounds and Bioactivities of Ginger (Zingiber officinale Roscoe). Foods 2019, 8, 185.
32. Li, X.; Jin, F.; Lee, H.J.; Lee, C.J. Recent Advances in the Development of Novel Drug Candidates for Regulating the Secretion of Pulmonary Mucus. Biomol. Ther. 2020, 28, 293–301.
33. Gholamnezhad, Z.; Keyhanmanesh, R.; Boskabady, M.H. Anti-Inflammatory, Antioxidant, and Immunomodulatory Aspects of Nigella Sativa for Its Preventive and Bronchodilatory Effects on Obstructive Respiratory Diseases: A Review of Basic and Clinical Evidence. J. Funct. Foods 2015, 17, 910–927.
34. Gholamnezhad, Z.; Shakeri, F.; Saadat, S.; Ghorani, V.; Boskabady, M.H. Clinical and Experimental Effects of Nigella Sativa and Its Constituents on Respiratory and Allergic Disorders. Avicenna J. Phytomed. 2019, 9, 195.
35. Shu, G.; Xu, D.; Ran, C.; Yin, L.; Lin, J.; Fu, H.; Zhang, W.; Bai, S.; Peng, X.; Zhao, X.; et al. Protective Effect of Dietary Supplementation of Bupleurum Falcatum L Saikosaponins on Ammonia Exposure–Induced Ileum Injury in Broilers. Poult. Sci. 2021, 100, 100803.
36. Li, X.Q.; Song, Y.N.; Wang, S.J.; Rahman, K.; Zhu, J.Y.; Zhang, H. Saikosaponins: A Review of Pharmacological Effects. J. Asian Nat. Prod. Res. 2018, 20, 399–411.
37. Cheng, P.W.; Ng, L.T.; Chiang, L.C.; Lin, C.C. Antiviral Effects of saikosaponins on human coronavirus 229E in vitro. Clin. Exp. Pharmacol. Physiol. 2006, 33, 612.
38. Li, C.; Chen, J.; Yuan, W.; Zhang, W.; Chen, H.; Tan, H. Preventive Effect of Ursolic Acid Derivative on Particulate Matter 2.5-Induced Chronic Obstructive Pulmonary Disease Involves Suppression of Lung Inflammation. IUBMB Life 2020, 72, 632–640.
39. Introduction to (Quantitative) Structure Activity Relationships—OECD. Available online: https://www.oecd.org/chemicalsafety/risk-assessment/introductiontoquantitativestructureactivityrelationships.htm (accessed on 7 March 2022).

40. Tong, W.; Welsh, W.J.; Shi, L.; Fang, H.; Perkins, R. Structure-Activity Relationship Approaches and Applications. Environ. Toxicol. Chem. 2003, 22, 1680–1695.
41. Duque, C.; Castellanos, L.; Tello, E. Structure-Activity Relationship (SAR) Studies to Maximize the Activity of Compounds Isolated from Octocorals. In Corals in a Changing World; IntechOpen Ltd.: London, UK, 2018.
42. Vanommeslaeghe, K.; Hatcher, E.; Acharya, C.; Kundu, S.; Zhong, S.; Shim, J.; Darian, E.; Guvench, O.; Lopes, P.; Vorobyov, I.; et al. CHARMM General Force Field: A Force Field for Drug-like Molecules Compatible with the CHARMM All-Atom Additive Biological Force Fields. J. Comput. Chem. 2010, 31, 671–690.
43. Pires, C.T.A.; Scodro, R.B.L.; Cortez, D.A.G.; Brenzan, M.A.; Siqueira, V.L.D.; Caleffi-Ferracioli, K.R.; Vieira, L.C.C.; Monteiro, J.L.; Corrêa, A.G.; Cardoso, R.F. Structure-Activity Relationship of Natural and Synthetic Coumarin Derivatives against Mycobacterium tuberculosis. Future Med. Chem. 2020, 12, 1533–1546.
44. Asfaw, H.; Laqua, K.; Walkowska, A.M.; Cunningham, F.; Martinez-Martinez, M.S.; Cuevas-Zurita, J.C.; Ballell-Pages, L.; Imming, P. Design, Synthesis and Structure-Activity Relationship Study of Wollamide B; a New Potential Anti TB Agent. PLoS ONE 2017, 12, e0176088.
45. Hou, X.M.; Wang, C.Y.; Gerwick, W.H.; Shao, C.L. Marine Natural Products as Potential Anti-Tubercular Agents. Eur. J. Med. Chem. 2019, 165, 273–292.
46. Lago, J.H.G.; Toledo-Arruda, A.C.; Mernak, M.; Barrosa, K.H.; Martins, M.A.; Tibério, I.F.L.C.; Prado, C.M. Structure-Activity Association of Flavonoids in Lung Diseases. Molecules 2014, 19, 3570–3595.
47. Delclaux, C.; Azoulay, E. Inflammatory Response to Infectious Pulmonary Injury. Eur. Respir. J. 2003, 22, 10s–14s.
48. Santana, F.P.R.; Pinheiro, N.M.; Mernak, M.I.B.; Righetti, R.F.; Martins, M.A.; Lago, J.H.G.; Lopes, F.D.T.Q.D.S.; Tibério, I.F.L.C.; Prado, C.M. Evidences of Herbal Medicine-Derived Natural Products Effects in Inflammatory Lung Diseases. Mediat. Inflamm. 2016, 2016, 2348968.
49. Timalsina, D.; Pokhrel, K.P.; Bhusal, D. Pharmacologic Activities of Plant-Derived Natural Products on Respiratory Diseases and Inflammations. BioMed Res. Int. 2021, 2021, 1636816.
50. Gong, J.H.; Cho, I.H.; Shin, D.; Han, S.Y.; Park, S.H.; Kang, Y.H. Inhibition of Airway Epithelial-to-Mesenchymal Transition and Fibrosis by Kaempferol in Endotoxin-Induced Epithelial Cells and Ovalbumin-Sensitized Mice. Lab. Investig. 2013, 94, 297–308.
51. Wang, C.; Zhou, J.; Wang, J.; Li, S.; Fukunaga, A.; Yodoi, J.; Tian, H. Progress in the Mechanism and Targeted Drug Therapy for COPD. Signal Transduct. Target. Ther. 2020, 5, 248.

52. Bansal, S.; Chhibber, S. Curcumin Alone and in Combination with Augmentin Protects against Pulmonary Inflammation and Acute Lung Injury Generated during Klebsiella pneumoniae B5055-Induced Lung Infection in BALB/c Mice. J. Med. Microbiol. 2010, 59, 429–437.
53. Yoon, J.H.; Baek, S.J. Molecular Targets of Dietary Polyphenols with Anti-Inflammatory Properties. Yonsei Med. J. 2005, 46, 585–596.
54. Santangelo, C.; Scazzocchio, B.; Filesi, C. Polyphenols, Intracellular Signalling and Inflammation. Ann.-Ist. Super. Di Sanita 2007, 43, 394–405.
55. Park, J.Y.; Ko, J.A.; Kim, D.W.; Kim, Y.M.; Kwon, H.J.; Jeong, H.J.; Kim, C.Y.; Park, K.H.; Lee, W.S.; Ryu, Y.B. Chalcones Isolated from Angelica Keiskei Inhibit Cysteine Proteases of SARS-CoV. J. Enzym. Inhib. Med. Chem. 2016, 31, 23–30.
56. Goc, A.; Sumera, W.; Rath, M.; Niedzwiecki, A. Phenolic Compounds Disrupt Spike-Mediated Receptor-Binding and Entry of SARS-CoV-2 Pseudo-Virions. PLoS ONE 2021, 16, e0253489.
57. Dorsch, W.; Wagner, H. New Antiasthmatic Drugs from Traditional Medicine? Int. Arch. Allergy Appl. Immunol. 1991, 94, 262–265.
58. Liu, C.; Yang, N.; Song, Y.; Wang, L.; Zi, J.; Zhang, S.; Dunkin, D.; Busse, P.; Weir, D.; Tversky, J.; et al. Ganoderic Acid C1 Isolated from the Anti-Asthma Formula, ASHMITM Suppresses TNF-α Production by Mouse Macrophages and Peripheral Blood Mononuclear Cells from Asthma Patients. Int. Immunopharmacol. 2015, 27, 224–231.
59. Liu, C.; Dunkin, D.; Lai, J.; Song, Y.; Ceballos, C.; Benkov, K.; Li, X.M. Anti-Inflammatory Effects of Ganoderma lucidum Triterpenoid in Human Crohn's Disease Associated with Downregulation of NF-KB Signaling. Inflamm. Bowel Dis. 2015, 21, 1918–1925.
60. Shi, Q.; Liu, Z.; Yang, Y.; Geng, P.; Zhu, Y.Y.; Zhang, Q.; Bai, F.; Bai, G. Identification of Anti-Asthmatic Compounds in Pericarpium citri reticulatae and Evaluation of Their Synergistic Effects. Acta Pharmacol. Sin. 2009, 30, 567–575.