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REVIEW ARTICLE

Recent Advances in Phytoleads for Management of Respiratory Disorders

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ABSTRACT

Respiratory disorder is one of the common disorders related to the respiratory tract. In regards, to the development of resistance against the drugs now in use, respiratory disorders become a significant major challenge in the health sector. For respiratory illness treatment, many phytoleads or phytoconstituents are traditionally used and for their efficacy, few have been found with optimistic results. In this review, all the phytoleads or phytoconstituents have anti-inflammatory activity, and some of them possess antioxidant activity too. All are used to treat respiratory tract inflammation. Curcumin was used as an anti-asthmatic also. The results of this study show that for the cure of respiratory system disorders, phytoleads or phytoconstituents are used.The use of Phytoleads nowadays provide benefit in the discovery of new drugs for future targets.

Keywords: COVID-19, isolated compound, NDDS for phytoleads, phytoleads, respiratory diseases

INTRODUCTION

Pulmonary disorder is of the most causes of morbidity and mortality overall. They are separated by airflow restriction, emphysema, bronchoconstriction, and mucus hypersecretion. Heredity, tobacco consumption, environmental damage, inhaling of hazardous particles, occupational toxins, and specks of dust have all been connected to the development of respiratory illness. Some disorders are moderate to lethal and life-threatening such as tuberculosis and pneumonia.[1]

ANGIOGENESIS-RELATED DISORDERS IN LUNGS

Angiogenesis is the process by which new capillary blood vessels grow in the body. It is a biological predisposition that aids in wound healing and the formation of new tissue. The body can regulate angiogenesis during neovascularization by achieving a perfect balance of growth and inhibitory agents. When there is an imbalance, either fewer or more blood vessels form.[2,3]

Improper angiogenesis is a contributing factor to some diseases. In both cases, abnormal blood vessel growth, whether excessive or insufficient, is responsible for the development of fatal diseases including cancer, skin disorders, hyperglycemia, coronary heart disease, hemorrhage, age-related blindness, and pulmonary diseases.[4]

Low immune performance, unfavorable climatic conditions, unbearable air pollution, overexposure to smoking and certain other harmful chemicals, and the existence of such fungi, pathogens, and infectious agents are all major causes of respiratory problems. The two types of vascularization found in the lungs are the bronchial vasculature, which is related to the thoracic aorta, and the bronchial network, which is involved in the formation of the air\blood barrier of tissue which is found in the lung.[5]

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Lung tissue produces two growth factors VEGF AND FGF-2 that are essential to the building or structure of lung tissue. Increased expression of VEGF and FGF-2 in histopathologic structure is triggered by the stimulation of such a chronic inflammation flood when lung tissue is exposed to unbearable airborne pollutants, too much smoke, as well as other poisonous fumes, which is a major cause of abnormal angiogenesis in the lung and eventually leads to the progression of lung cancer.[6]

COPD is linked to the decreased capillary length of blood capillary, blood density, and lack of oxygen, which is pursued by hypoxia-inducible factors (HIF-1) modulation, which is important in the formation of angiogenesis.[7]

Bronchial asthma, as a result of inflammation and mucus plug formation in the respiratory tract, which is linked to excessive angiogenesis, is associated with airway congestion and demodulation.[8] In the aforementioned situations, cytokines, cell adhesion molecules, growth factors, vasoactive peptides, proteolytic enzymes (metalloproteinase), and plasminogen activators all play a role in the activation of the EGFR/PI3/AKT/mTOR pathways. These pathways are activated, causing endothelial growth regulators to be activated and VEGF and FGF-2 to be overexpressed.[3] Angioedema, chronic inflammation, pulmonary fibrosis, bronchospasm, decreased ventilation, and harm to alveolar capillaries are all symptoms of lung diseases such as bronchial asthma and COPD idiopathic pulmonary arterial hypertension (PAH). The insufficient delivery of oxygen to the lung tissue is caused by several situations. Additional systems aim to recover oxygen saturation or assist the organism in adapting to oxygen deprivation if an inadequate amount of oxygen persists for an extended time, hypoxia is mediated by HIFs, which are composed of two subunits: HIF1/2 and HIF-1.[9] After a time of decreased oxygen availability, HIF-1 is stabilized through post-translation modification. The subunit gets split off and binds to the subunit as soon as it stabilizes. This heterodimer then attaches to promoters of hypoxia response VEGF target genes, causing them to be transcribed. The production of VEGF is stimulated by the HIF-1 in lung tissue by activating the epidermal growth factor (EGF). NO synthase is the enzyme, particularly the NOS3\ NO isoform that controls nitric oxide synthesis. This isoform is required for VEGF-driven hypoxia or AKT phosphorylation of the eNOS isoform at serine 1117 can both trigger angiogenesis.[10] The etiology of numerous lung illnesses is influenced by uncontrolled inflammation. The bronchial epithelium and the microenvironment of the lungs change as a result of inflammation.[11]

Transforming growth factor-beta, platelet-derived growth factor (PDGF), interleukin 6 (IL-6), and IL-8 are proinflammatory signals that stimulate the signaling pathways and transcription factor of transcription 3 (STAT3) pathway. Angiogenic mediators, such as VEGF, cause STAT3 phosphorylation, which leads to angiogenesis [Figure 1].[12]

Furthermore, hypoxia also stimulates VEGF gene expression by activating cyclooxygenase, an inducible enzyme in lung tissue that catalyzes the synthesis of prostaglandins (PGs) from arachidonic acid.[13]

In asthma and COPD, oxidative stress increases the expression of inflammatory genes, which leads to airway inflammation. During inflammatory airway inflammation, nuclear factor-kappa is a significant regulator of cytokine activity.[14]

ASTHMA

This chronic respiratory condition of the airway causes sudden severe pain in the chest, dyspnea, difficulty in breathing, coughing, and sneezing asthma is triggered by genetic and environmental factors and is activated by airway irritants such as passive smoking, airborne pollutants, sensitivities, parasitic infections, anxiety, mold spores, and termites. When an allergen is breathed into the lungs and attaches to IgE antibodies on mast cells, the mast cells generate histamine and leukotrienes (LT), triggering an asthma attack. Smooth muscle cells or bronchial smooth muscle cells contract as a result of these biologically active mediators. The concentration of eosinophils causes the lumen of the bronchi to constrict. Repeated attacks or a buildup of eosinophils in the lungs induce bronchial damage. It is difficult to breathe in the late stages of asthma attacks, which occur when the smooth muscle cells in the bronchi contract,

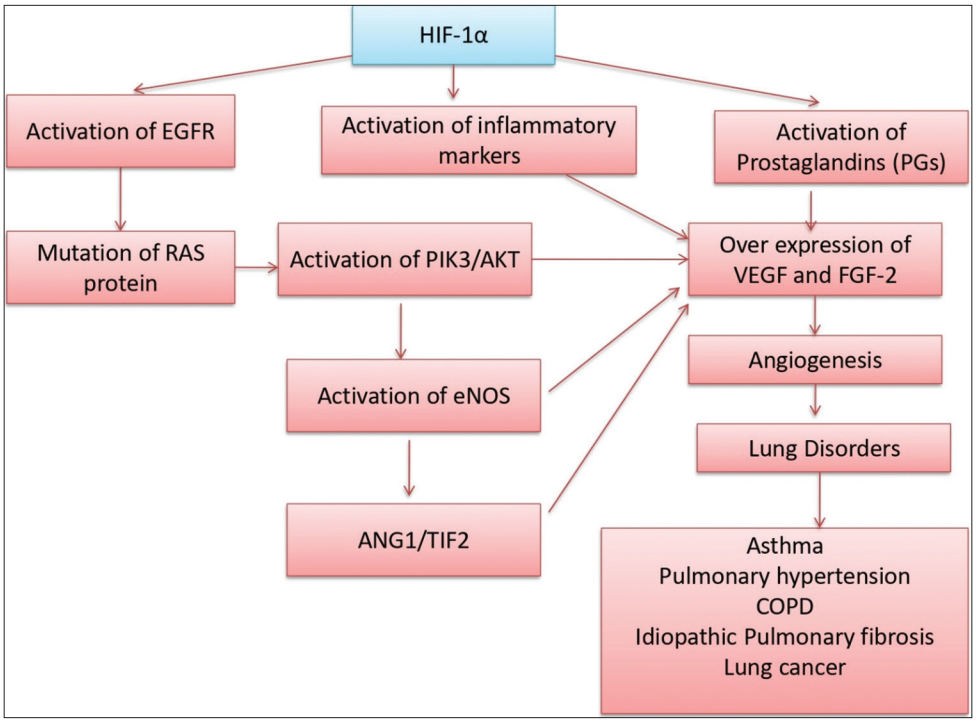

Figure 1: Angiogenesis in lung disorder

causing the airways to become irritated and swollen. Asthma symptoms include eosinophilia, edema, hypersecretion of mucus, bronchial epithelial injury, and hyperactivity. Appears to have changed in bronchoalveolar lavage fluid, as well as changes in airway epithelial cells, eosinophils, macrophages, dendritic cells, T-helper type 2 cells, IgE-secreting B-cells, and mast cells, are among the cell types involved in disease development.[15]

COPD

COPD is caused by a variety of pathogenic causes that are closely interrelated. As COPD advances, epithelial cells create inflammatory mediators and infiltrate inflammatory cells such as neutrophils, macrophages, and T lymphocytes in the lungs as COPD progresses. Tumor necrosis factor (TNF), IL-1, IL-1 beta, and IL-6, as well as chemokines such as IL-8, are critical inside the pathogenic process because they activate and attract circulating cells. Epithelial cells produce inflammatory mediators and infiltrate inflammatory cells in the lungs, such as neutrophils, macrophages, and T lymphocytes. Proinflammatory TGF has been linked to the creation of airway fibrosis, which can respond to airway damage. Several techniques for inhibiting these cytokines have been proposed, with IL-1 and IL-8, major compounds of the inflammasome.[16] The inflammasome acts as molecular platform and signaling platforms that stimulate the processing of ILs and activate inflammatory caspases, and additional inflammasome components being indicated as prospective targets. IL-1 beta is stimulated by the inflammasome, which is responsible for the detection of danger signals by the immune system.[17]

The role of reactive oxygen species (ROS) in the development of COPD is significant.[18] Tobacco smoke includes significant oxidants levels and produces a variety of free radicals, also together with ROS, which amplify the inflammatory response and progress COPD to the severe stage. COPD could be treated using enzymes such as nuclear erythroid-2-related factor 2, NADPH oxidase, myeloperoxidase, and superoxide dismutase as a result of various oxidative stress-related molecules. MMP and neutrophil elastase are two enzymes that are particularly tightly regulated in COPD pathogenesis. Activation and increased synthesis of matrix metalloproteinases such as MMP-2, -9, and -12 have been linked to the development of

COPD in numerous studies.[19]

Sirtuins have recently been discovered to be important in COPD. COPD patients' lungs had a lower amount of sirtuin 1 expression. The activation of Sirtuin 1 and 6 has been linked to a reduction in COPD risk;[20] hence, sirtuin activators could be considered as potential COPD treatments. In their exhaled breath condensate, COPD patients have higher levels of LTB4 and PG E2 than healthy people.[21] A strong neutrophil chemoattractant is LTB4 and its concentration is similarly higher in COPD patients' sputum.[22] For the treatment of COPD, for lower LTB4 levels, 5-lipoxygenase inhibitors and antagonists of LTB4 have been discovered. COPD patients' airways and peripheral lungs have inducible nitric oxide synthase (iNOS) at a high-level patient.[23] NO, and its oxidant peroxynitrite, which is produced by iNOS, generate oxidative stress in the lungs. The use of a specific inhibitor to decrease iNOS was demonstrated to partially ameliorate pulmonary artery remodeling and functional impairment in a mouse model of smoke-induced emphysema.[24] Recent research suggests that disrupting signal transduction pathways may help in the COPD progression which is slow. The COPD-related transcription factor and inflammatory genes are regulated by several kinases. p38 mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) have been identified as promising candidates for selective inhibitor development. Inflammatory mediators such as IL-1, IL-8, and MMP are produced in a range of inflammatory cells when the p38 MAPK pathway is activated, exacerbating COPD symptoms. Inhibiting p38 MAPK was found to be successful in COPD patients with ≤2% blood eosinophils participated in a 6-month research trial found that inhibiting p38 MAPK was effective.[25]

In COPD lungs, the activity of PI3K-mediated signaling in macrophages and neutrophils is increased and it is engaged in inflammation and immune response. In a mouse smoke model, inhibiting particular isoforms of PI3K were reported to diminish pulmonary neutrophilia.[26]

As prospective COPD therapies, various PI3K inhibitors targeting nuclear factors which are transcription factors contributing to the encoding of the numerous inflammatory genes, as well as related kinases like IB kinase have also been investigated.[27]

PNEUMONIA

Pneumonia is a respiratory tract illness in which pus builds up in the alveoli, causing inflammation in one or both lungs. Pneumonia depends on whether it is caused by bacteria, viruses, or fungi. Pneumonia could be moderate, chronic, and even fatal. *Moraxella catarrhalis, Haemophilus influenza, Chlamydophila pneumonia, Klebsiella pneumonia, Staphylococcus aureus, and Legionella pneumophila, these all species that are causing agents for pneumonia.* Fungal pneumonia is PCP which is caused by the fungus *Pneumocystis Jirovecii*, which is most common in immune-compromised persons. Adenovirus, varicella-zoster, influenza virus, or respiratory syncytial virus are responsible for viral pneumonia.[28,29]

TUBERCULOSIS

An airborne infectious illness is tuberculosis that affects not only the respiratory tract but also other organs, that is, the spine and brain. The most prevalent bacteria which is responsible for tuberculosis is Mycobacterium tuberculosis.[30] *Mycobacterium tuberculosis* complexes that cause TB include *Mycobacterium Bovis* and *Mycobacterium Mocroti*. The most frequent signs of active tuberculosis include a rise in body temperature, sweating during in night, losing weight, and persistent bloody sputum in cough. The treatment for tuberculosis is time-consuming and needs a long course of antibiotics,[31] and genetic criteria are also used to recognize the bacteria and treat it.[32]

PAH

PAH seems to be a long-term illness marked by blood pressure between the lungs and the heart is high, which results in increased systemic pulmonary vascular resistance (PVR) and, eventually, cardiac arrest. Difficulty breathing, chest tightness, and heart palpitations are prevalent PAH symptoms

caused by vascular remodeling due to excessive cell proliferation and a low rate of apoptosis.[33]

PAH is categorized by the World Health Organization based on the following symptoms.

a. PAH is considered a rising pressure in an artery produced by a blockage in the lung's small arteries
b. PAH as a result of heart illness on the left side
c. Hypoxia is responsible for the development of PAH
d. Clot formation in the lungs prevents that blood flow is chronic thromboembolic PAH
e. PAH can be caused by a variety of metabolic, systemic, or hematologic issues.[34]

When an imbalance occurs between antiangiogenic factors and angiogenic factors, it will cause the obliteration of lung vessels in PAH. Although PAH is usually regarded as the role of angiogenic agents such as VEGF and its receptors which involve in the pathobiology of PAH remains uncertain, because it is a proangiogenic illness. Due to pulmonary vasoconstriction, lung artery remodeling, or both PVR is raised in severe instances of PAH.[35]

IDIOPATHIC PULMONARY FIBROSIS (IPF)

IPF is a long-term disorder in which the parenchyma of the lungs is fibrosis. Repeated cell injury in alveolar epithelial and upregulated lung fibroblast proliferation creates this condition. These fibroblasts grow uncontrollably eventually changing into myofibroblasts in the interstitial space, which contain ECM proteins. TNF, IL-1, IL-13, TGF, CTGF, PDGF, VEGF, and FGF-2 as well as their signaling pathways, are hypothesized involve in the pathophysiology of IPF.[36]

LUNG CANCER

Lung cancer is a potentially fatal disease caused by uncontrolled lung cell proliferation. Lung cancer usually begins in the bronchi, then spreads to surrounding tissues and throughout the body. They are two forms of lung cancer large cell lung cancer and small-cell lung cancer (SCLC) is more aggressive, has a faster growth rate, and can spread to other organs. Slow-growing cancer is Non-SCLC (NSCLC). Based on the tissue in which the tumor develops, NSCLC is again divided.[37] The most prevalent kind of NSCL is adenocarcinoma (40%), squamous cell carcinoma (25–30%), and large cell carcinoma (10–15%). Some previous studies have discovered genetic anomalies that widely help in NSCLC development. The primary disease EGFR activation has been linked to the progression of lung cancer and ALK gene arrangement. VEGF has been identified as a possible lung cancer target. The activation of EGFR signaling is intimately connected to that of VEGF. VEGF inhibits numerous proangiogenic and proliferative signaling pathways by inhibiting the activity of tyrosine kinase.[38] The aberrant lung cell proliferation in our person is likewise due to overexpression of VEGF, according to a clinical investigation by Masato Shingyoji. Various studies investigated the effects of anti-VEGF medication, particularly end star in combination with cisplatin, Lewis lung cancer rat's VEGF expression.[39]

WHY MEDICINAL PLANTS ARE THE BETTER CHOICE??

In today's drug discovery age, a wide range of chemically produced compounds are approved by regulatory authorities and released into the market, with good therapeutic benefits, yet this medication has major side effects that can be fatal. Due to fluctuations in plasma drug concentrations, there are peaks and valleys, conventional therapy delivers non-target ability in the body, and allopathic therapy can be hampered by frequent dose delivery, resulting in poor patient compliance. Nowadays, herbal medicines are used by around 80% of the world's population for the care of health and other purposes demonstrating the breadth of their application. Herbal medications also have a broader spectrum of pharmacological activity and less-lethal problems with fewer side effects. Herbal medicines have reclaimed their reputation as effective and safe treatments for lung illnesses, with controlled clinical research proving their efficacy and safety. A current global study has also provided useful information on the herbal alternatives' particular mode of action.[1]

PHYTOCONSTITUENT OR PHYTOLEADS

Phytoconstituents are the moiety of a chemical that occurs naturally in plants and is responsible for a variety of organoleptic and medicinal properties. Chemical moieties include alkaloids, glycosides, polyphenolic compounds, and other secondary metabolites. This century has seen a lot of research on phytoconstituents and their health implications. Due to their significance in the prevention of severe life-threatening diseases such as cancer, cardiovascular disorders, and respiratory infections, the outcomes of their treatment are of particular interest. Scientists will remain interested in phytoconstituents, because these diseases are currently the leading causes of death. Phytoconstituents are gaining popularity as a supplement and alternative medicine due to their numerous health benefits, including antioxidant, anti-inflammatory, and immunomodulatory properties.[1]

- It is appealing to consider inhalation treatment as a novel drug delivery method. Scientists are concentrating their efforts on utilizing this non-invasive therapy to treat a variety of extrapulmonary disorders. Because they are constantly exposed to an oxygen-rich environment, the lungs are vulnerable to oxidative stress. To avoid lung tissue damage, the lungs contain antioxidant defenses, for example, vitamins C and E, carotene, heme oxygenase, superoxide dismutase, glutathione, and uric acid. Natural antioxidants include phytoconstituents such as flavonoids, which are polyphenolic chemicals. Anti-inflammatory and antibacterial effects have been discovered in polyphenolic compounds.
- A nebulizer, a pressurized metered dosage inhaler, a soft mist inhaler, or a dry powder inhaler (DPI) are used to deliver antioxidants and anti-inflammatory substances in lung tissue straight to the airway. DPIs can improve the physicochemical and biological properties of phytoconstituents and ensure that larger medication concentrations are delivered at the deposition site.[1]

Many phytoconstituents with anti-asthmatic activity have been discovered to date, and numerous plants have these components to treat asthma-related issues. Curcuma longa, Aerva lanata, Cynodon dactylon, Piper betle, Lepidium sativum, Curculigo orchioides, and Casuarina equisetifolia are the plants in question.

THE DEMONSTRATED ACTIVITY OF MEDICINAL PLANTS TREATING PNEUMONIA

1. Echinops adenocaulos
2. Verbascum fruticulosum
3. Parietaria Judaica
4. Urtica urens
5. Beta vulgaris.[30]

THE DEMONSTRATED ACTIVITY OF MEDICINAL PLANTS TREATING TUBERCULOSIS

1. *Anogeissus leiocarpa*
2. *Terminalia avicennioides*
3. *Capparis brassii*
4. C*ombretum* spp.
5. *Solanum torvum*
6. *Galenia africana*
7. *Allium sativum*
8. *Allium cepa*
9. *Cinnamomum verum*
10. *Acalypha indica*.[30]

NDDS FOR PHYTOLEADS

Phytoleads are to be incorporated into suitable delivery agents for improved and site-specific actions or local actions. A novel drug delivery system enhances the bioavailability of particular molecules and acts locally hence reducing the adverse kinds of effects. The allopathy system, it is the most trending system of drug delivery. It is also used in phytopharmaceuticals for delivery. Phytosomes, liposomes, niosomes, ethosomes, nanoparticles, nano gels, and many more are used.[40]

RECENT WORK IN PHYTOLEADS

Recent Global Pandemic COVID-19

At present, the contagious sickness known as COVID-19 is threatening the entire planet and infecting millions of people. It is a very hazardous issue for health; hence, within a small period, many kinds of research are being processed and many works of the literature suggest the pathophysiology of COVID-19 virus.[41]

Covid-19 is caused by the most common RNA virus that has the largest single-strand RNA that affects the human pulmonary system. There are now no available medical options to cure the virus, which is increasing the mortality rate across the country. Because India is a stronghold for traditional herbal remedies, finding a method the combat COVID-19 is a distinct possibility. Although most coronavirus infections in humans have moderate clinical symptoms, the world's two primary beta-coronaviruses, severe acute respiratory syndrome coronavirus Middle East respiratory syndrome (MERS-CoV) and coronavirus (MERS-CoV), are responsible for at least two serious epidemics.[42]

The SAR-CoV virus is a serious respiratory infection that affects a person's upper respiratory system, which includes the throat, nose, and sinuses, as well as the lower respiratory tract (windpipe and lungs).[43] MERS-CoV is communicable virus that transmitted person to person or animal also, so it is also known as zoonotic virus.[44]

Anatomy of COVID-19

Coronaviruses have positive-sense RNA viruses containing spherical casings that belong to the Coronaviridae family and the Nidovirales order.[45] CoVs are RNA viruses with enormous genomes ranging from 26 to 32 kilobases in size. The CoV genome encodes four key structural proteins: spike (S) glycoprotein, nucleocapsid phosphoprotein, membrane glycoprotein, and envelope glycoprotein. As in the virus envelope of the SARS-CoV-2 virus, the hemagglutinin esterase protein is also found. To generate a fully functional virion, all of these proteins are necessary. The S glycoprotein, which forms a homotrimer protruding from the virus surface, is involved in the virus's entry into the host cell. S1 is involved in the virus's binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell, whereas S2 is important in the virus's fusion with the cellular membrane.[46]

Pathophysiology of the COVID-19

This coronavirus is an encapsulated single-stranded positive RNA virus. The virus enters the host with receptors that are identified by the viral spike protein. There are 16 non-structural proteins (NSPs) in the host cell after entry, such as NSP-12 and RNA-dependent RNA polymerase. This is required for full-length viral RNA synthesis. NSP works in the same way as host cell suppression mRNA does, possibly reducing the host's immune response.[47] In humans, the receptor for COVID-19 was determined to be ACE2. The pathophysiology of the virus shows that it can damage the ACE2 site.[48] The virus's impacts cause normal cell activity to be disrupted. The enzyme is a zinc-containing enzyme that is involved in the conversion of angiotensin 2 to angiotensin 1, as well as the cleavage of bradykinin, dynorphin A, and ghrelin.[49] When evaluating viral entry at the site, ACE2 disrupts the function of cleavage. This will result in a rise in bradykinin levels. According to the literature, bradykinin can also cause a cough. A chemical mediator is bradykinin, which causes smooth muscle contraction and enhanced capillary permeability, resulting in edema in the lungs and disruption in alveolar gas exchange function.[50]

Current Management Option

The principal instrumental management strategies are now oxygen supplementation and mechanical ventilation. At present, anti-retroviral medications include ritonavir\lopinavir (400 mg/100 mg in every 12 h), anti-malarial chloroquine (500 mg in every 12 h), and anti-malarial hydroxychloroquine (200 mg in every 12 h) are used. Alpha-interferon is another method that has been presented.[41]

COVID-19 PREVENTION AND TREATMENT WITH MEDICINAL PLANTS AND PHYTOCONSTITUENTS

Piper nigrum L. (Kaali Mirch, Black Pepper)

Extract has many pharmacological activities such as antiviral, anti-oxidant, anti-thyroid, anti-tumor, antibacterial, anti-inflammatory, and immunological modulator, its phytoconstituents can be used. A few of them phytoleads are used as antiviral agents such as piperine, feroperine, piperylin, N-trans-feruloylpiperidine, piperoleine A, dehydropipernonaline, pipernonaline, piperidine, and they are.[45]

Ocimum sanctum (Holy Basil, Tulsi)

Tulsi is known as the "Elixir of Life" in Ayurveda for its healing properties and capacity to treat a variety of maladies such as bronchitis, pyrexia, rheumatism, asthma, skin diseases, parasite and microbial infections, stomach and hepatic disorders, and more. Tulsi has therapeutic potential as an immune system booster, antibacterial, anti-diabetic, anti-carcinogenic, anti-viral, anti-inflammatory, cardioprotective, and other medicinal properties.[51] Apigenin and ursolic acid are the main antiviral compounds in Tulsi extract.[45]

Nigella sativa (Black Cumin, Black Seed, Kalonji)

In black cumin, the active phytochemical is thymoquinone, which is accountable for the majority of its medicinal benefits. In terms of antiviral capabilities, the oil and seeds of *N. sativa* have been proven to have viricidal properties against a variety of dead viruses with the hepatitis C virus and HIV.[52]

Cinchona officinalis (Cinchona Quinine)

Chloroquine's antiviral effects are investigated first against HIV, now use against SARS-CoV-1, which shares structurally similarities with the new SARS-CoV-2. This is structurally similar to the newly discovered SARS-CoV-2. The chloroquine-treated group has been proved to be better than the control respondents in comparison to shortening the disease course, improving lung imaging results, lowering pneumonia exacerbation, and increasing virus-negative seroconversion with no side effects in clinical trials.[53,54]

Sambucus nigra (Elderberry)

It boosts the immune system of the body.[49]

Tinospora cordifolia (Giloy, Guduchi)

Biologically relevant phytochemicals that have immunomodulatory functions in the human body include lactones, alkaloids, glycosides, steroids, sesquiterpenoid, diterpenoid, phenolics, polysaccharides, aliphatic compounds, and flavonoids. It has anti-inflammatory, anti-allergic, antimicrobial, anti-osteoporotic, anti-diabetic, anti-arthritic, anti-stress, anti-cancer, anti-HIV, heart tonic, wound healing, bitter tonic, carminative, and blood purifier properties. *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, *Shigella flexneri*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Enterobacter aerogene*, *Serratia marcesenses,* and *Proteus vulgaris* were found to have broad-spectrum antimicrobial efficacy against methanol extract of Gil Tinosporin, tetrahydropalmatine, choline, magnoflorine, and palmatine are among the alkaloid components that protect against aflatoxin-induced nephrotoxicity.[45]
Tulsi (6 leaves) + Ginger (1/2 tsp.) + Giloy (Size of one Bhibdi) + Kali mirch (4-6 seeds)
Grind all the ingredients together and then it will be drunk like herbal tea or mixed with honey. It can help with coughs, fevers, and immunity. Giloy juice should be administered orally. This help to increase resistance power of body.[46]

Azadirachta indica (Margosa Neem)

It is having various pharmacological activities. The whole plant is full of therapeutic value. Various extracts and isolated constituents are used for numerous activities. Aqueous neem leaf extract has been shown to have antiviral activity against measles, Chikungunya, and Vaccinia virus.[55]

Syzygium aromaticum (Clove)

It contains phenolic components such as eugenol, eugenol acetate, thymol, carophyllene, and gallic acid gas a lot of promise for cosmetic, medicinal, food, and agricultural uses. It contains anti-inflammatory, anticancer, antioxidant, antifungal, antiviral, and antibacterial. Eugeniin, a phytochemical, has been shown to have potent antiviral properties. Eugeniin has antiviral characteristics because it inhibits the virus DNA polymerase enzyme, which prevents DNA synthesis.[56,57]

Pranax ginseng: Triterpenoids, protopanaxadiols, protopanaxtriols and steroidal saponins also known as ginsenoid are the primary chemical components of ginseng. Antibacterial and other possible activities are attributed to polysaccharides and proteins, particularly for viruses that cause respiratory infections in humans. Ginseng possesses antiviral efficacy due to its ability to prevent viral attachment, membrane penetration of the virus, and reproduction of the virus.[43]

Glycyrrhiza glabra (Liquorice, Licorice)

Glycyrrhizin is chemically a triterpene saponin and it is a possible phytochemical that can be used against COVID-19, from a pharmacological standpoint. The binding of ACE2, as well as downregulating proinflammatory cytokines and preventing the prevention of intracellular ROS buildup, thrombin, hyperproduction of airway exudates, and activating endogenous interferon, are all discussed in the study.[58] By inhibiting viral DNA polymerase, glycyrrhizic acid (GL) suppressed Epstein–Barr virus multiplication in Vero cells with an IC50 value of 0.004 mM. In Vero cells with a SI of 67, GL displayed antiviral action against SARS-CoV by lowering virus proliferation and blocking virus penetration and adsorption.[59]

Andrographis paniculatais (Kalmegh)

In recent times, using *in silico* methods, researchers looked at the Andrographolides have an inhibiting effect on SARS-CoV-2 proteases.[60]

Allium sativum (Garlic)

Antiviral properties could assist to lessen the severity of a cold, flu, or COVID-19 infection, as a result, garlic helps to boost the immune system and fight infections and other ailments. Allicin, a broad-spectrum antibiotic, is present.[61] It is said to boost immunological health by increasing boosting white blood cells such as NK cells and macrophages.[62]

Zingiber officinalis (Ginger)

It is having phytoconstituent such as zingerone,6-gingerol, paradol, phellandrene, zingiberene, and 6-shagaol. Ginger is having strong immune-boosting properties in the addition to antiviral properties.[46]

Piper betel (Betel vine)

It is having immunity-boosting activity.[49]

Curcuma domestica (Turmeric)

Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the key phytochemicals found in turmeric. Germacrone, turmerone, atlantone, and zingiberene are the principal essential oils found in turmeric.[46] Turmeric sales have surged in the United States as a result of its antiviral qualities. Turmeric aids in the natural cleansing of the respiratory tract: it also aids in the fight against infection, and its anti-inflammatory effects provide comfort for cold and flu sufferers. Lower immunity is well acknowledged to be a risk in and of itself and curcummini is particularly beneficial in resolving such difficulties and improving the immune system which is more helpful in SARS-CoV-2 treatment.[63] Curcu, reduces inflammation, relieves congestion, and pain, so assisting people with bronchial difficulties such as sinusitis and sinus respiration in improving their breathing process. Congestion, cough, bronchial asthma, colds, and shortness of breath are the most common upper respiratory tract issues, which affect youngsters and the elderly. Breathing becomes difficult as a result of the inflammation of the airways.[45]

Withania somnifera (Ashwagandha, Indian Ginseng)

Withanone lowers the electrostatic component of the ACE2- receptor-binding domain (RBD) complex's binding free energy, blocking or weakening COVID-19 entrance and infectivity. It is also been claimed that SARS-CoV-2 used its spike protein RBD to entrap host cells in the human body, notably ACE 2 and RBD complex. In the upcoming fight against COVID-19 infectivity, Ashwagandha may be the best option among a variety of medicinal herbs.[45] The roots of Ashwagandha have a lot of antiviral properties.[64] Pineapple/Ananas comosus: bromelain refers to a group of sulfhydryl proteolytic enzymes derived from the stemor fruit. Bromelains have antiplatelet and anti-inflammatory properties, as well as the ability to reduce substance P and edema. Bromelain tends to lower bradykinin levels. Bromelain is also an effective cancer fighter and immunomodulator.[45]

Haritaki/Terminelia Chebula

Haritaki has antihistaminic properties. Haritaki also has antiviral action, lysosomal membrane stabilization activity, phenolic content, and the ability to block sialic acid, making it a possible source of antiviral activity.[65]

Other Medicinal Plants Can Be Used

Lemongrass leaves (*Cymbopogeon citratus*) or essential oil, mint leaves (*Mentha*) or essential oil, Lemon (*Citrus*), ginger (*Zingiber officinale*), cloves (*Syzygium aromaticum*), wild honey (*Apis mellifera*), *Tripterygium regelii* Sprague, and Takeda, *Ecklonia cava*.[66]

Other Phytoconstituent Can Be Used

Acacetin, auraptene, cardamonin, daidzein, epicatechin, glabridin, herbacetin, isoxanthohumol, and taxifolin hydrate.[67] Antiviral action was demonstrated by decreasing the SARS-CoV 3C protease (3Cpro).[68] While MERS-CoV 3Cpro activity was decreased by herbacetin, isobavachalcone, quercetin 3-βD-glucoside, and helichrysetin,[44] while Celastrol, Pristimerin, Tingenone, Iguesterin,[69] Dieckol, Eckol, Triphloretol-A, Dioxinodehydroeckol,2-Phloroeckol, Phloroeckol, Phlorofucofuroeckol-A, Fucodiphloroethol G showed activity against SARS-CoV.[70]

SPIKE PROTEINS AND RECEPTORS OR THE INHIBITION OF VIRUS

The target receptor in the SARS-CoV-2 spike glycoprotein is recognized by a RBD. The receptor ACE2 is where SARS-CoV-2 prefers to bind (ACE-2).[71] Furin inhibits the attachment and fusion of mouse hepatitis coronavirus spike proteins during infection.[72] Emodin prevents coronavirus entrance by preventing the spike protein from interacting with ACE-2.[73] Secondary metabolites from medicinal plants, such as hesperidin, pectolinarin, cannabinoids, rhoifolin, diosmin, apiin, diacetylcurcumin, and epigallocatechin gallate, are biological active against the main spike and protease glycoproteins of SARS-CoV-2, so all available antiviral drugs must be screened against COVID-19 is being developed to speed up the development of therapeutic options for the treatment of COVID-19 infection.[74]

Recent Ongoing Work

Medicinal plants are used as potent nucleocapsid phosphoprotein inhibitors against COVID-19. Moreover, in this research, phytoleads are used for different computer-aided drug designing, molecular modeling, homology modeling, and different kinds of software-related SAR studies are ongoing as synthetic molecules. Because phytoleads are also a better choice for treating SARS-COV-2.[75]

CONCLUSION

Plants and their phytoleads are much better options due to their great therapeutic value and have a minimum number of adverse effects compared to allopathic drugs. The entire scenario crisis moved to natural products as a result of the COVID-19

outbreak because till now many antiviral drugs were used to treat COVID-19, but not a single drug can give promising results, although they reduce the severity of the disease and could decrease the rate of mortality. However, they also showed some adverse effects. The pharmacological effects of these drugs are also temporary for many infections. Moreover, the maximum chance is also for reoccurring disease. Phytoleads is always a better choice because they are potent and the concept of phytoleads is new because plants have many therapeutic values, this is so ancient principle, but those phytoleads, which are responsible for the particular illness, are a choice of interest. Moreover, now, all researchers are going through this. Scientists are working very much on these phytoleads.

Future Prospective

The work of the researcher is to investigate these all phytoleads for each health-related issue ailment. Hopefully, in the future, all kinds of disorders must be treated using these phytoleads with potential novel drug delivery systems. Computer-aided drug designing will also be very much efficient for these phytolead-related discoveries.

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