

The Role of Natural Nrf Activators in Respiratory Diseases

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Abstract: Respiratory diseases are those which are related to airways and lung disorders. Nrf2 (67kDa pzip CNC transcription factor) nuclear erythroid 2-related factor is a transcription factor with complex multi-domain proteins which regulates the anti-oxidant response element (ARE) driven cyto protective protein expression. It is believed that Nrf2 activation reduces the systemic inflammation, lowers the oxidative stress and improves the mitochondrial function and this can be useful in treating various respiratory diseases like chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis(IPF), bronchopulmonary dysplasia (BPD), asthma, infection related to respiratory organs, acute respiratory distress syndrome(ARDS), lung cancer etc. Nrf2 activation helps to prevent the tissue or cell damage occurred by oxidative stress. under stress, kelch like ECH associated protein (cysteine rich protein), a natural inhibitor of Nrf2, traps Nrf2 in cytoplasm thus degrades Nrf2 by 26s proteosome. stress impairs the protein to target Nrf2 for ubiquitination, degrade and uses Nrf2 (newly synthesized) to translocate to nucleus and bind with ARE. These activators can be activated by exercise, fasting or by restriction calories or also by intake of natural nutrients. Nrf2 activators used commonly are Curcumin (lung cancer), anti-oxidants found in green tea, Resveratrol(Pneumococcal infections, ARDS,COPD, Lung cancer), vitamin E (Asthma), Sulforaphane (Asthma,IPF, lung cancer), Emodin (IPF, IAV infections), Quercetin (IPF), derivative BHBA(lung cancer), Cinnamaldehyde, Bixin,tBHQ (RSV infection, ARDS) etc.

Keywords – Nrf activator, Respiratory diseases, Sulforaphane, Asthma, COPD

1 INTRODUCTION

Respiratory diseases: Respiratory diseases are the non-communicable diseases which are related to airway and lung disorders for example- Chronic obstructive pulmonary disease(COPD),Idiopathic pulmonary fibrosis (IPF), Bronco-pulmonary disease(BPD), Chronic or severe asthma, infections related to respiratory organs, Acute respiratory distress syndrome(ARDS), Lung cancer etc. In the recent research it was found that most prevalent respiratory disease is COPD (3.9% global prevalence) and asthma (3.6% global prevalence) and these diseases accounted for 3.9 million deaths in 2017(an increase of 18.0% since 1990)[1,2].

To date researchers have found that Nrf2 deletion effects in high susceptibility and severity in insults in quite number of fashions of respiratory diseases. Transcription component nuclear erythroid -2 related factor (Nrf2) is a fundamental regulator of anti-oxidant response element (ARE) pushed cytoprotective protein expression. The activation of Nrf2 signaling performs fundamental role in preventing cells and tissues from harm brought on by means of oxidative stress. Under the unstressed conditions, herbal inhibitor of Nrf2,Kelch-like-ECH- associated protein 1 (Keap1), traps Nrf2 in cytoplasm and assist the degradation of Nrf2 by using the 26S proteosome. Nevertheless, stresses along with relatively oxidative microenvironments, impair the capacity of Keap1 to target Nrf2 from ubiquitination and degradation and set off newly synthesized Nrf 2 to translocate to the nucleus to bind with ARE. Due to constant publicity to external environment , together with various pollutants and different oxidants , the redox stability maintained by means of Nrf2 is fairly essential to airways [3].

1.1Pathophysiology of Respiratory Diseases:

It is a proliferative carcinoma of the breast tissue. Signs include changes in form, dimpling of the skin, leakage of the nipple, etc. “Symptoms of spread may include swelling of the breast tissue, lumps associated with pain and discoloration. Proliferative breast lesions include hyperplasia in the duct, adenosis of sclerosis, fibroadenomas, and papillomasintraductal”. Canal carcinoma induces hydroxyl radicles. “Hydroxyl radicles cause lesions in ductal carcinoma and contribute to cancer pathogenesis. BC epidemiology indicates that in the absence of cyclic progesterone production, estrogen stimulation produces breast carcinogen, as the alpha estrogens receptor plays a vital role in the normal development of breast cells”[6].

1.2 Asthma: It is an inflammatory disease in which airway gets inflamed which leads to airway hyper-responsiveness, over-production of mucus and obstruction of airway. The risk factors include genetic predisposition, atopy, gender, indoor allergens, outdoor allergens, smoking. Allergens include dust mite, fungal spores, tree pollens etc, viral infections

(rhinovirus), pharmacological agents (ACE inhibitors), air pollutants (Sulfur dioxide), physical factors (hyperventilation) and stress. Asthma symptoms generally occurs when lining of airway swells, muscles tightening, and mucus is filled in airway which reduces the airflow in bloodstream. In asthmatic patients, inflammation occurs in airway and thus results in difficulty in breathing. Asthma occurs in 2 phases – early phase and late phase. In early phase, plasma cells release IgE antibodies and they are sensitized and these antibodies respond to various triggers mentioned above. When a pollutant is inhaled, cytokines are released by mast cells and degranulation occurs. Histamine, leucotrienes and prostaglandins are released from mast cells and contracts the smooth muscles and thus results in airway tightening. The interleukins (IL-3, IL-4, IL-13) are produced by Th2 lymphocytes and sustain inflammation. Eosinophils and basophils are survived by IL-3 and IL-4 and IL-13 contributes to remodeling. After few hours, late phase occurs, various cells like neutrophils, eosinophils, memory T cells, basophils are localized to lungs which causes constriction and inflammation[4].

Airway hyper-responsiveness is the one of the features of asthma occurred by various stimuli. This can be due to excess histamine release from mast cells. The excess of intracellular calcium as well as vagal tone results in smooth muscle contractility. These changes results in difficulty in breathing. The excess secretion of mucus causes a person difficult to breathe. Increase in thickening of membrane is caused by collagen and obstruction occurs.

Remodeling: Epithelial cell transition to mesenchymal thus increases smooth muscle content results in remodeling. Cell adhesion as well as polarity with tight ends is lost by epithelial cells and further reformats cells to form to mesenchymal cells. Eosinophils can cause further remodeling because of release of TGF- β and various cytokines by interacting of mast cells. Remodeling may worsens the asthmatic inflammation if not correctly managed and treated[4][5].

1.3 Lung cancer: Also called as Bronchogenic carcinoma, is a condition in which there is formation of tumors in lung parenchyma or in bronchi. 90% of lung cancer cases are due to smoking and other factors are exposure to various metals like nickel, arsenic, polycyclic aromatic hydrocarbons, chromium, asbestos, tar, genetics etc. Idiopathic fibrosis is also a cause of lung cancer. Its Patho-physiology is complex and yet incompletely understood.

Excessive exposure to carcinogens – Small cell (SCLC) and non-small cells lung cancer (NSCLC) both arises from different cells. SCLC arises from Neuro-endocrine cell and further causes metastasis, para-neoplastic syndrome (ectopic Cushing syndrome) or causes growth of tumor that results in distal obstruction and infection (cough, dyspnea, post obstructive pneumonia, wheezing etc. SCLC responds to chemotherapy and NSCLC arises from epithelial cells which also called growth of tumor, peripheral tumor that irritates airway and infiltrate pleura (cough, dyspnea, pleuritic chest pain, pan coast tumor) also can cause slower metastasis, less response to chemotherapy, surgical method needed (tests for EGFR mutation). NSCLC does not responds to chemotherapy[6].

1.4 Chronic obstructive pulmonary diseases (COPD): A disease with high rate of morbidity and mortality. It is the obstruction of airway (chronic obstructive bronchitis and emphysema) which can be confirmed by spirometry. Risk factors like smoking and environmental factors (indoor pollutants present in air) leads to shortness of breath due to air trapping. The process involves oxidative stress and imbalance of protease and anti-proteases (alpha1 trypsin deficiency). Emphysema, is a lung disease that involves the damage to alveoli (small, thin walled air sacs) of lungs. Alveolar sacs (gas exchangers) weaken and they eventually break which reduces surface area of lungs and causes destruction of radial traction which leads to narrowing of airway and bronchitis. Excess production of mucus by goblet cells results in narrowing of airway and thus plug formation occurs. These plugs remain in lungs (epithelial cells) because of non- functioning of ciliary function which leads to bacterial growth.

Acute exacerbations of COPD are due to viral pneumonia or bacterial pneumonia. Excessive inflammation as well as air trapping require corticosteroid treatment and also bronchodilator treatment in cases of chronic obstructive pulmonary diseases[7][8].

1.5 Bronchopulmonary dysplasia:

Broncho-pulmonary is a condition which affects the lungs of infants results in difficulty in breathing. Lungs do not develop normally. It includes two factors, pre-natal and post- natal. The antenatal factors are genetic susceptibility, intrauterine growth restriction (IUGR), chorioamnionitis, pregnancy induced hypertension disorders, smoking, and Natal risk factors include gestational age, weight, oxidative stress, hyperoxia, mechanical ventilation, infections, patent ductus arteriosus, respiratory microbial dysbiosis. Mechanical ventilation injury and antenatal factors predisposes lungs to broncho-pulmonary dysplasia. This leads to inflammation with increase in pro-inflammatory (interleukins like IL-6, IL-8, TNF-alpha, tumor necrosis factor and growth factors and also angiogenic factors include (angiopoietin 2). Patho-physiology of new broncho pulmonary dysplasia is distinguished by pulmonary vascular simplification and gas change abnormalities, function of

respiratory and lung volume so, BPD patients may have vascular diseases as well as airway disorders[9][10].

1.6 Idiopathic pulmonary fibrosis (Ipf) –Another name for Idiopathic pulmonary fibrosis is cryptogenic fibrosingalveolitis, is a type of disorder of lung scarring and cause is still unknown. The scarring of lungs rapidly increases and results in difficulty in breathing due to reduced oxygen. It can easily be diagnosed by biopsy. The continuous injury to alveolar epithelium results in fibrosis. The risk factors are smoking, infections (viral), chronic aspiration. With continuous injury of epithelium results in activation of fibroblasts and dys-regulates repair of epithelium and this leads to increase of matrix deposition in interstitium and thus scars the lung, and destroys lung architecture which further causes pulmonary fibrosis. the destruction of lungs impair the gas exchange with hypoxic respiratory failure, an advanced stage[11].

2. Drugs used along with mechanism of actions:

2.1 Asthma: Drugs used in asthma are bronchodilators, anti-inflammatory, leukotriene antagonists.

Beta2 agonists: Albuterol: It is used while acute exacerbation as it relaxes bronchial muscles. Salmeterol: Used in prophylaxis (long-acting beta-2 agonist).

Methylxanthines: Theophylline- Acts as bronchodilator that inhibits phosphodiesterase (decrease in cAMP hydrolysis, increases cAMP levels), releases Ca^{++} from sarcoplasmic reticulum. It has narrow therapeutic index moreover metabolised by cytochrome P-450, thus adenosine action is blocked.

Muscarinic antagonists: Ipratropium (long-acting): These drugs produce bronchodilation by blocking cholinergic constrictor tone, mainly acts on large airways.

Corticosteroids: Beclomethasone, Fluticasone (first line therapy)-Synthesis inhibition of cytokines and inactivates transcription factor (NF- κ B) which induces TNF- α production.

Antileukotrienes: Montelukast, Zafirlucast- It blocks Leucotriene receptors which causes bronchodilation, suppresses inflammation, reduction of sputum. These are used for prophylactic therapy of mild or moderate asthma.

Anti-IgE monoclonal therapy: Omalizumab- Free IgE is neutralized without activation of mast cells so, level of IgE in plasma reduces, thus causes inhibition of mast cell IgE mediated histamine.

Herbal drugs used in treatment of asthma are:

Bronchodilators: *Ginkobiloba*, *Lepidium sativum*, *Ephedra sinica*, *Gardenia latifolia*.

Mast cell stabilizers: *Cassia torosa*, *Allium cepa*, *Menthapiperita*, *Curcuma longa*, *Tinosporacordifolia*.

Anti- allergics: *Magnolia officinalis*, *Inularasemosa*, *Citrus unshiu*, *curcuma longa*.

Anti- inflammatory agents: *Aloe vera*, *Calotropisprocera*, *Indigoferatinctoria*, *Ferulasinica*.

Immuno-modulatory drugs: *Plantago ovata*, *Trichiliaglabra*, *Withaniasomnifera*.

The consumption of herbal drugs is increasing day by day as they do not have any toxic effects or show drug resistance. It has been estimated that 80-85% of world's population rely on herbal medicines. Many of natural herbal treatments are available for to treat asthma which include vitamins, minerals, and herbs to relieve symptoms and to prevent from further attacks. There are many medicinal plants which have anti-asthmatic potential are – *Acorus calamus* (Removes catarrhal matter and phlegm from bronchial tubes), *Asystasiagangetica*, *Allium sepa*, *Acasiacatechu*, *Atropa belladonna* (Anti-spasmodic), *Cannabis sativa* (Broncodilator), *Calotropisprocera*, *Daturametel* (Anti-asthmatic, anti-spasmodic, anti-tussive, broncodilator), *Cinnamomum cassia* (Anti-edemic properties), *Ephedra sinica* (Short term broncodilator), *Ganodermalucidum* (Anti-allergic), *Camellia sinensis* (Anti-allergic), *Glycyrrhizaglabra* (Anti-inflammatory), *Morus alba* (Anti-asthmatic, anti-tussive, diuretic, expectorant), *Moringaoleifera*, *Nigella sativa*, *Lobelia inflata* (Treats spasmodic asthma), *Sidacordifolia*, *Oscimum sanctum* (Anti-histamic), *Solanummelongena* (Bronco-spasmogenic effect), *Plantago major* (Anti-spasm), *Piper longum*, *Withaniasomnifera* (Anti-inflammatory), *Ulmusrubra* (Reduces thickness of mucus), *Zingiberofficinalis* (Natural expectorant), *Tinosporacordifolia* (Reduces brochospasms)[1,12].

Apart from herbal and conventional drugs, Nrf2 activators which are used to treat asthma are :

1) Sulforaphane : It inhibits diesel exhaust particle (DEP)-stimulated inflammation in airway epithelial cells, and suppresses ovalbumin and Cl_2 -induced allergic airway inflammation in mice and thus improves broncho-protective response against MCh (Methacholine) in asthma patients[13][14].

2) Vitamin E: It protects against asthma induced by IgE and alleviates exacerbation (asthma) stimulated by ozone in OVA-induced murine model[3].

2.2 Lung cancer: FDA approved non-small cell lung cancer.

Angiogenesis inhibitors: Bevituximab (Avastin)- Phosphatidylserine inhibitors (stops tumor growth from growing their own blood vessels).

Anti-metabolites: Gemcitabine, Methotrexate – Blocks the synthesis of DNA/RNA.

Anti-microtubule agents: Docetaxel, paclitaxel – Microtubule assembly, prevents spindle formation.

Photosensitizing agents: porfimer- cell damage by porfimer is consequence of propagation of radical reactions, porfimer absorbs light to form porphyrin excited state and transfer of spin porfimer to molecular oxygen which generate singlet oxygen. Radical reaction forms superoxide and hydroxyl radicals. Also, tumor death occurs through ischemic necrosis secondary to vascular occlusion that appears to be mediated by thromboxane A2 release.

Tyrosine kinase inhibitors: crizotinib, eriotinib, gefitinib – Inhibits the kinases involved in growth factor receptor transduction.

Herbal treatment for lung cancer

Extracts of herbal plants play an important role in treatment of cancer. There are various plants used in treatment of lung cancer depending upon types of lung cancer are *Withaniasomnifera*, Pomegranate (pro-apoptotic effect, DNA fragmentation, inhibits oxidative damage of DNA, anti-oxidant property, inhibits histone deacetylases, cytotoxicity of cancer cells), *Curcuma longa*, Green tea, *Lithospermum radix* [15], *Rasagenthilehyam, plumbagin*, *E.succirubrum*, *Podophyllum emodi*, (SCLC), *Taxus brevifolius* (Microtubule disruptor, block mitosis, induces apoptosis, microtubules are polymerized and stabilised, disruption of spindle formation, inhibition of translational machinery), *Mappia foetidissima*, *Glycyrrhiza uralensis* [16].

The Nrf2 activators which can treat lung cancer are:

- 1) Curcumin: It exerts anti-initiating effect in B[a]P-treated mice [17].
- 2) Sulforaphane: It exerts suppressive effect on B(a)P initiated lung carcinogenesis mice [3] [18].

2.3 Chronic obstructive pulmonary disease: No cure is there for COPD but some medication can help to reduce inflammation.

Traditional therapy:

Bronchodilators: Short acting bronchodilators - Albuterol, Levalbuterol, Ipratropium etc. Prescribed for emergency situation. Bronchodilators target beta-2 receptors, that is G-protein coupled receptor in lung airway.

Long acting bronchodilators: Formoterol, Acclidinium, Salmeterol, Tiotropium, Roflumilast, Arformoterol - Helps to treat COPD for longer period of time.

As bronchodilators target beta-2 receptor that is G-protein coupled receptor in lung airways, when these beta-2 receptors are activated, smooth muscles relax and patient gets better airflow.

Corticosteroids: Fluticasone, Budesonide, Prednisolone - Reduces inflammation by improving lung function by acting on multiple cell types and mediators involved in inflammation and airflow obstruction.

Methyl-xanthines: Theophylline, these are phosphodiesterase inhibitors, increases cAMP, and causes bronchodilation, Adenosine receptor antagonist, increases diaphragmatic contraction, thus stabilization of mast cell membrane.

Combination of drugs (Triple therapy - an inhaled corticosteroid, 2 long acting bronchodilators) - fluticasone/vilanterol/umeclidinium.

Roflumilast (Phosphodiesterase-4 inhibitor): It inhibits PDE4 leading to accumulation of cAMP within inflammatory and structural cells important in pathogenesis of COPD.

Mucocactive drugs: Carbocysteine, Erdosteine, N-acetylcysteine. They increase ability to expectorate sputum or decrease mucus secretion.

Anti-biotics: Azithromycin, Erythromycin.

New pharmacotherapies for COPD: Reduce the frequency of exacerbations.

1- New LAMA monotherapy; Acclidinium, Glycopyrronium, umeclidinium.

2- New LABA monotherapy: Indacaterol, Vilanterol, Olodaterol.

3- New LABA+LAMA combination therapy: Umeclidinium and Vilanterol, Tiotropium and olodaterol.

4- New LABA+ICS combination therapy: Vilanterol and Fluticasone, Formoterol and Fluticasone.

5- New oral agents- Azithromycin, Moxifloxacin, Simvastatin [19].

Herbal drugs used in treatment of COPD

Herbal therapies are used in treatment of root cause of disease and exponential growth has been observed in field of herbal treatments as these have fewer toxic effects. Various plants and herbal extracts used in treatment of COPD are *Atropa belladonna* (Acts on parasympathetic nervous system and has anti-muscarinic effect that inhibits smooth muscle contraction and reduces mucus secretion), *Arctiumlappa* (Anti-inflammatory), *Plantago major* (anti-inflammatory), *Mikaniaglomerataspreng* (anti-inflammatory), *Equisetum arvense*(anti-inflammatory), oral ginseng(anti-inflammatory, anti-oxidant activity)[20].

The Nrf2 activators used to treat COPD are:

- (1) Sulforaphane: it counteracts CSE induced oxidative injury in epithelial cells(alveolar) and augments bacteria phagocytosis by alveolar macrophages[21].
- (2) Resveratrol : It protects from CSE induced lung injury[3].

2.4 Bronchopulmonary dysplasia

Diuretics(Furosemide) It acts on ascending Loop of henle and blocks chloride transport and it also decreases interstitial edema and pulmonary vascular resistance. Hence also decreases interstitial edema, and increases lymphatic flow and plasma oncotic pressure. Overall respiratory status is improved by furosemide like oxygenation, pulmonary mechanics etc. Thiazides affect renal tubular excretion and are considered less potent than loop diuretics. Potassium and bicarbonate excretion also occur which has triggered the use of thiazides in conjunction with spironolactone, an aggressive inhibitor of aldosterone. A small variety of controlled trials analyzing the use of thiazide diuretics and spironolactone in BPD have generated mixed outcomes with urine output increasing.

Bronchodilators: Albuterol is an inhaled beta 2 agonist that is endorsed for treatment of BPD with robust issue of reversible bronchospasm. It has been associated with non-permanent upgrades in pulmonary resistance and lung compliance secondary to bronchial clean muscle rest. In summary, long term efficacy has not been set up and tolerance may advance with extended use.

Methyl-xanthines: Caffeine cure for the prevention of apnea of prematurity and BPD is presently the standard of care in most neonatal intensive care devices. The expanded muscle contractility may stabilize the chest wall and improve functional residual capacity facilitating successful extubation. After many findings, it has been concluded that caffeine remains fashionable scientific approach in prevention of BPD.

Corticosteroids: Dexamethasone (Inhaled) which facilitates extubation and reduces combined endpoint of BPD and reduces the incidence of ROP and PDA, and Sildenafil(systemic) which is a phosphodiesterase inhibitor that increases cyclic guanosine mono-phosphate concentration, and thus promotes pulmonary vasodilatation.

The Nrf2 activators to treat BPD are:

- (1) Curcumin: It attenuates hyperoxia lung injury in rats(newborn)
- (2) Sulforaphane: It inhibits the lung inflammation induced by hyperoxia in newborn mice[3].

2.5 Idiopathic pulmonary fibrosis: Approved drugs for IPF are:

1-Anti-fibrotic agents (Anti-scarring agents) : Pirfenidone ,Nintedanib.

2- Corticosteroids: Prednisolone- Reduces inflammation in lungs .

3-Anti-oxidants: N-acetylcysteine.

4-Other potential drugs are proton pump inhibitors which block the stomach from producing acid. And immune-suppressants such as azathioprine and mycophenolate which treat autoimmune disorders and help prevent the rejection of transplanted lung.

The Nrf2 activators used to treat idiopathic pulmonary fibrosis are:

1)Sulforaphane: It has anti-fibrosing effect in IPF fibroblasts and even under TGF-stimulation[22].

2)Quercetin: It induces anti-oxidant defense and suppress the inflammation and inhibits the TGF-beta induced fibrosis in fibroblasts[3].

3. Natural Nrf2 activators and their mechanisms

The common Nrf2 activators are Curcumin (From turmeric –potent Nrf2 activator), Resveratrol (from grapes), Quercetin(from onion), Sulforaphane(from broccoli, cauliflower, kale, cabbage, sprouts), green tea, and other sources are raspberry , pomegranate, and dark chocolate[23].



Fig 1. Broccoli (A source of sulforaphane)

Sulforaphane: A sulfur - rich compound. It is a compound within isothiocyanate group of organo-sulfur compounds. It is produced when the myrosinase enzyme converts glucoraphanin (aglucosinolate) to sulforaphane on damage to plant, that allows the two compounds to mix and react. Young sprouts of cauliflower and broccoli are rich in glucoraphanin.

Biological source: It is found in cruciferous vegetables like broccoli, cabbage, cauliflower, kale, sprouts, mustard greens, water cress etc.

Family- Brassicaceae family

Genus- Brassica oleracea

Sulforaphane in treatment of COPD:

COPD, a persistent pulmonary illness characterized through irreversible airflow limitation, emerged as 1/3rd most popular cause of death. COPD is associated with small airway obstruction and tissue remodeling, which could result in magnificent inflammation and lung parenchyma destruction in response to various stimuli and moreover oxidative stress has been identified as essential predisposing component that debts for the pathogenesis of COPD, and cigarette smoking containing rich oxidants has long been seen as a dominant environmental risk thing for COPD.

In healthful smokers, to cope with such excessive oxidant burden, there is significant expand in anti-oxidants defenses, among which Nrf2 is most relied. This reliance may moreover be evidenced by using transient Nrf2 expression caused via CS in human airway cells. However reduced degrees of Nrf2 and its stabilizers DJ 1(PARK7) in lung tissues of COPD patients have been observed, and a couple of human research have tested that the NRF2-KEAP1-BACH1 equilibrium in lung and alveolar macrophages is reduced in population of aged humans who smoke and are COPD patients. In a finding, Nrf2 deficient mice are more susceptible to cigarette smoke publicity and toughens extra severe lung emphysema and apoptosis, and activity of anti-oxidant enzymes is repressed.

Additionally, the relationship between Nrf2 and COPD has been addressed in vitro: Nrf2 knockdown will increase 10% CS exposure (CSE), whilst Nrf2 over-expression protects cells from apoptosis brought by means of using CSE.

Novel therapies, like Nrf2 activators may promise COPD patient therapy, as they have potential to protect against cigarette smoke. For example- sulforaphane which can augment the phagocytosis of bacteria (like as PA and NTHI isolated from COPD patient) by alveolar macrophages from patients of COPD, but absence of ability in Nrf2 siRNA –transfected macrophages is observed, and similar results got in wild-type and Nrf2 knockout mice. The further study showed, Nrf2 dependent bacterial clearance by sulforaphane might be associated with Nrf2 mediated regulation of scavenger receptor MARCO (Collagen structure) but does not depend on anti-oxidant glutathione. These researches suggest that the sulforaphane protects against COPD patients[3].

4 Various Nrf2 formulations available in market:

Quercetin formulations for respiratory disorders:

- 1) Amazing a nutrition (Dietary supplement) Quercetin bromelain capsules.
 - For Improving respiratory health and supports cardiovascular health.
 - Antioxidant- Helps reduce free radical damage.
 - Supports Healthy inflammatory response and immune system.
- 2) Ultimate protector+ (100% Non-GMO vitamin c super powerful high-ORAC anti-oxidants and multiple plant based Nrf2 activator.



-Anti-inflammatory.

-Anti-oxidant property.

- 3) Quercetin solid lipid microparticles: An inhalational formula for inhalational lung delivery[24].

Curcumin formulations for respiratory disorders:



- 1) Mother tree (nutra)- Curcumin turmeric extract.
 - Controls asthma, cough, bronchitis, and cold.
 - anti-inflammatory and anti –oxidant property[25].
- 2) Dr. liers original hank and brains (Mighty multi-vite!)- Dietary supplement 120 veggie capsules.



-Anti-oxidant and anti-inflammatory property.

Sulforaphane formulations for respiratory disorders:

- 1) Pure therapro (Nrf2 BOOST) Dietary supplement 60 acid-resistant vegetable capsules.



- Powerful Nrf2 genetic pathway activator.
- Myrosinase –active for sulforaphane conversion.
- Anti-oxidant and detoxification support formula[26].

5. CONCLUSION AND FUTURE PERSPECTIVES:

It can be concluded from the latest review of literature that the natural Nrf activators significantly minimize the risk of respiratory diseases and successfully treat them. Further the use of natural Nrf activators is suggested to prevent and treat various diseases like asthma, COPD, bronchitis, lung cancer, BPD, IPF, etc. Nowadays, more focus is towards the safest and natural management of respiratory disorders to outweigh the benefits of a drug over side-effects. As conventional dosage form has several limitations like less bioavailability, short duration of action, high toxicity profile, less solubility, patient non-compliance. All these limitations have been overcome by the use of natural Nrf activators like “sulforaphane, curcumin, quercetin,” etc.,

6. REFERENCES

- [1] Labaki W W and Han M L K 2020 Chronic respiratory diseases: a global view *Lancet Respir. Med.* **8** 531–3
- [2] Craig Li Fang A links open overlay panel S. K 2017 Pathophysiology of respiratory diseases *Anaesth. Intensive Care Med.* **Volume 18** Pages 10-15
- [3] Liu Q, Gao Y and Ci X 2019 Role of Nrf2 and its activators in respiratory diseases *Oxid. Med. Cell. Longev.* **2019**
- [4] O’Byrne D M M M 2010 Recent Advances in the Pathophysiology of Asthma
- [5] Stockdale T 2003 Asthma [2] *Nutr. Health* **17** 81–3
- [6] Neal I Lindeman 1, Philip T Cagle, Mary Beth Beasley, Dhananjay Arun Chitale, Sanja Dacic, Giuseppe Giaccone, Robert Brian Jenkins, David J Kwiatkowski, Juan-Sebastian Saldivar, Jeremy Squire, Erik Thunnissen M L 2013 download 823–59
- [7] Joseph Milic-Emili*, 1 M P and E D 2008 Pathophysiology of Chronic Obstructive Pulmonary Disease *Curr. Respir. Med. Rev.* 250–7

- [8] Corry-Anke Brandsma, 1, 2 Maarten Van den Berge, 2, 3 Tillie-Louise Hackett, 4, 5 Guy Brusselle, 6, 7 and Wim Timens 2020 copd2 *J. Pathol.* 624–35
- [9] CuevasGuamanbBinoyShivannab A links open overlay panelRenjithkumarKalikkot T 2017 Bpd (1) *Respir. Med.* **Volume 132** Pages 170-177
- [10] & J S H and Rehan V K 2018 Bpd_2 **volume 196** pages129–138
- [11] Marina R Hadjicharalambous 1 M A L 1 2020 ipf2 *Natl. Cent. Biotechnol. Inf.*
- [12] Prasad R, Lawania R D and Gupta R 2009 PHCOG REV . : Review Article Role of Herbs in the Management of Asthma Abstract : *Online 3* 247–58
- [13] Jack A. Elias, Chun Geun Lee, Tao Zheng, Bing Ma, Robert J. Homer and Z Z 2003 New insights into the pathogenesis of asthma *J. Clin. Investig.* 291–7
- [14] Robert H. Brown, Curt Reynolds, Allison Brooker P T & J W F 2015 Sulforaphane improves the bronchoprotective response in asthmatics through Nrf2-mediated gene pathways *Respir. Res. Vol.*
- [15] Velayudem Ravichandiran H N ahamed and S N 2017 Natural Flavonoids and Lung Cancer *Nat. FLAVONOIDS LUNG CANCER Velayudem*
- [16] Greenwell M and Rahman P K S M 2015 Medicinal Plants: Their Use in Anticancer Treatment. *Int. J. Pharm. Sci. Res.* **6** 4103–12
- [17] Hironori Satoh, Takashi Moriguchi, Keiko Taguchi, Jun Takai, Jonathan M. Maher, Takafumi Suzuki, Paul T. Winnard, Venu Raman, Masahito Ebina, Toshihiro Nukiwa M Y 2010 nrf2-deficiency-creates-a-responsive-microenvironment-for-metasta-3 *J. Carcinog.* **31** 1833–43
- [18] Di Zhang, 1 Jonathan Rennhack, 2 Eran R. Andrechek, 2 Cheryl E. Rockwell 1 and Karen T. Liby1 2018 Identification of an Unfavorable Immune Signature in Advanced Lung Tumors from Nrf2-Deficient Mice. 1535–52
- [19] Montuschi P 2006 Pharmacological treatment of chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* **1** 409–23
- [20] Ram A, Balachandar S, Vijayananth P and Singh V P 2011 Medicinal plants useful for treating chronic obstructive pulmonary disease (COPD): Current status and future perspectives *Fitoterapia* **82** 141–51
- [21] Deepti Malhotra 1, Rajesh Thimmulappa, Ana Navas-Acien, Andrew Sandford, Mark Elliott, Anju Singh, Linan Chen, Xiaoxi Zhuang, James Hogg, Peter Pare, Rubin M Tudor S B 2008 Decline in NRF2-regulated antioxidants in chronic obstructive pulmonary disease lungs due to loss of its positive regulator, DJ-1 *Natl. Libr. Med.* 592-604.
- [22] Anon 2017 Protective_effect_of_forsythiaside_A_on_OVA_induced_asthma_in_mice_
- [23] Houghton C A, Fassett R G and Coombes J S 2016 Sulforaphane and Other Nutrigenomic Nrf2 Activators: Can the Clinician’s Expectation Be Matched by the Reality? *Oxid. Med. Cell. Longev.* **2016**
- [24] Ayoub Z and Mishra S 2018 Medicinal Plants As Natural Antioxidants : a Review Medicinal Plants As Natural Antioxidants : a Review *J. Bot. Soc. Univ. Saugor* **1** 100–7
- [25] SHARMA G and THAKUR N 2019 Curcumin – the Healing Herb: Properties and Future Prospective *Asian J. Pharm. Clin. Res.* **13** 4–9
- [26] Kim J K and Park S U 2016 Current potential health benefits of sulforaphane *EXCLI J.* **15** 571–7