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Review

Recent advances in respiratory diseases: Dietary carotenoids as choice of therapeutics

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ABSTRACT

A group of bioactive, isoprenoid pigments known as carotenoids is mostly present in fruits and vegetables. Carotenoids are essential for the prevention of physiological issues, which makes maintaining excellent health easier. They are effective functional ingredients with potent health-promoting properties that are widely present in our food and linked to a decrease in the prevalence of chronic diseases, including respiratory diseases. Respiratory infections are the primary cause of death and life-threatening conditions globally, wreaking havoc on the global health system. People rely on dietary sources of carotenoids to reduce a plethora of respiratory diseases such as chronic obstructive pulmonary disease (COPD), lung cancer, asthma, and so on. Carotenoids have received a lot of interest recently in several parts of the world due to their therapeutic potential in altering the pathogenic pathways underlying inflammatory respiratory diseases, which may improve disease control and have beneficial health benefits. This review aimed to provide a thorough understanding of the therapeutic potential of dietary carotenoids in the treatment of respiratory diseases and to identify possible candidates for novel therapeutic development.

1. Introduction

Respiratory diseases are medical conditions that interfere with how air-breathing animals exchange gases by disrupting the lungs and other respiratory tissues. They are also known as lung diseases [1]. But apart from the lungs, respiratory diseases also include conditions of all the respiratory organs, e.g., trachea, bronchi, bronchioles, alveoli, pleurae, pleural cavity, respiratory nerves and muscles. The prime breathing disorders are- asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer. The most common risk factors behind these diseases are- infection, direct or indirect intake of tobacco smoke, inhalation of radon, asbestos and other forms of air pollutants [2]. Respiratory infections wreak havoc on the global health system as they are the leading causes of death and serious illnesses [3]. About 3 million people die each year from moderate to severe COPD, making it the third greatest cause of death globally — and the numbers

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are rising [4,5]. Asthma, the most recurrent chronic disease of adolescence attacks 14% of children and around 334 million people worldwide and are becoming more prevalent in youngsters [6,7]. Acute lower respiratory tract infection is believed to kill about 4 million people annually and has been a primary cause of death and disability for decades in both adults and children, especially under 4 years old [8]. Youngsters affected by these infections are at the risk of developing chronic respiratory diseases later in their life. Influenza-related respiratory tract illnesses cost between 71 and 167 billion USD and kill between 250,000 and 500,000 individuals each year [9]. In 2015, 10.4 million people were affected and 1.4 million of them died due to Tuberculosis (TB) [10]. Lung cancer, the most recurrent fatal neoplasm in the world, kills 1.6 million people yearly, and the frequency is rising [11].

As people age, their lung function deteriorates, making breathing more challenging. It has been discovered that a diet high in carotenoids helps older people's lungs work better. There is no evidence that dietary carotenoids are correlated to pulmonary functions outside of β-carotene. Some researchers studied the association of carotenoid intake with FEV1% (forced expiratory volume in 1 s) and FVC% (forced vital capacity) as a percentage of predicted value, among 1616 men and women aged 35–79 years, living in western New York State and not having any respiratory diseases [12,13]. After modifying for the variables such as smoking, total caloric intake, and others, using multiple linear regressions, significant correlations between lutein/zeaxanthin and vitamins C and E and FEV1% and FVC % were noticed [14]. When all of these antioxidant vitamins were scrutinized at the same time, it was noticed that vitamin E had the strongest relationship with FEV1% and lutein/zeaxanthin had the strongest relationship with FVC %. Differences in forced expiratory volume in one second and forced vital capacity associated with a 1 standard deviation decrease in dietary vitamin E or lutein/zeaxanthin were equivalent to the effects of 1–2 years of age [15]. These findings affirmed the idea that carotenoids, vitamin C and vitamin E have a contribution in respiratory health. Many studies have unearthed that nutritious antioxidant vitamins including vitamin C, vitamin E, and β–carotene are linked to improved lung function [15]. Despite the extensive research about vitamins C and E, the data is still indecisive [16]. A number of cross-sectional studies have constructed a connection between ingestion of β-carotene and respiratory function [17], but information on rest of the carotenoids is rare. This scarcity of knowledge about more than 600 carotenoids full of antioxidant activity, present in our diet is unanticipated [18,19]. Grievink et al. came upon that, lung function in an older Dutch population was related to the blood levels of carotenoids i.e. lycopene, α-carotene, and β-carotene [20]. The level of carotenoids found in blood was found to be positively correlated with the respiratory function indices forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) in a sample of the general population. The most striking connection between the serum carotenoids lutein/zeaxanthin and cryptoxanthin is reported [21].

This review emphasizes to provide a comprehensive summary of the medicinal properties of dietary carotenoids against respiratory diseases and identifying promising candidates for novel drug discovery.

2. Carotenoids: an overview

Carotenoids are a group of more than 750 pigments which are synthesized organically by plants, algae, and photosynthetic microorganisms. Several plants or plant parts have yellow, orange, or red pigmentation as a result of these vividly colored molecules. The majority of the 40–50 carotenoids found in the human diet are found in fruits and vegetables [22], but they can also be obtained from molds, yeast and bacteria. Carotenoids are frequently found in standard concentration in body tissues of human and other animals, despite their inability to synthesize these molecules in vivo. The reason behind this presence is that, carotenoids are absorbed from the food, transferred and stored in the body [23,24]. The most familiar dietary carotenoids take in α-carotene, β-carotene, lutein, β-cryptoxanthin, lycopene and zeaxanthin [25,26]. α-Carotene, β-carotene and β-cryptoxanthin, commonly called Provitamin A carotenoids, can be transformed into retinol within the body. On the contrary, lutein, zeaxanthin, and lycopene are classified as non-provitamin A carotenoids as they cannot be converted to retinol. Though 90% of dietary α-carotene and 50% of dietary β-carotene are supplied by the common root vegetable, carrot, other root vegetables like beetroot, rutabaga, turnip, celeriac, and radish are not good source of carotenoids [27].

Since carotenoids are soluble in fat, cooking with oils or fats is a crucial factor in their absorption. Leafy vegetables with a deep green or orange color contain carotene, or provitamin A. Higher percentage of provitamin are linked with deeper hues [28,29]. Among the carotenoids, β-carotene is the most plentiful in foods and its provitamin A activity is also the highest. It is abundant in buriti (*Mauritia vinifera* Mart.) [30], tucum (*Acrocomia mokayáyba* Barb. Rodr.), bocaiva, acerola, mango, some pumpkin varieties, carrot, nuts, camu-camu (*Myrciaria dubia*), carrot noodles, rose hip fruits, and oil palm [26,30]. Only the tissues of plants and algae contain the red pigment lycopene. The most noticeable sources of lycopene nowadays are ripe tomatoes and their juices, soups, sauces, ketchup, even the processing waste and peel. Even greater amount of it is gained from cherry, guava, and guava products; comparable concentrations in watermelon and Thai papaya, and in smaller proportions in Solo and Formosa papaya varieties [31,32].

Lutein and zeaxanthin exist in green and deep green herbs such as broccoli, parsley, spinach and Brussels sprouts [33]. Acerola, pumpkin and common leafy vegetables are all great suppliers of lutein and β-carotene. The consumable flower of *Tropaeolum majus* L. 53 is a fantastic source of lutein, and it may also be present in large portions in caja (*Spondias lutea*) and camu-camu (*Myrciaria dubia*). *Chlorella vulgaris*, *Chlorella sorokiniana* MB-1, and the native microalgae *Scenedesmus obliquus* CNW-N are specimens of lutein producing microalgae. Pequi (*Caryocar villosum*) and the natural aquatic microalgae *Chlorella saccharophila* have prominent levels of zeaxanthin [34,35].

3. Therapeutic activity of carotenoids in respiratory diseases

3.1. Asthma

Asthma is a common inflammatory condition of the airways that causes the bronchi to tighten and swell, additionally producing excessive mucous. Due to this, breathing becomes hard and is accompanied by dyspnea, coughing, and expiratory wheezing. Some people may only experience asthma as a minor inconvenience [36–38], while a serious issue for others that forestalls their ordinary lives and in some cases even result in a severe respiratory disease. Even though asthma attacks can't be cured, their symptoms might be managed. It's crucial to keep records of signs and symptoms since the nature of asthma attacks might fluctuate over time and also varies from person to person. The common signs and symptoms are- shortness of breath, chest tightness, angina, wheezing when exhaling, sleep apnea, coughing and whistling. Attacks are exacerbated by a respiratory virus, such as a cold or the flu [39]. Increased oxidative stress and impaired antioxidant defenses are linked to asthma. Foods contain powerful antioxidants called carotenoids, which may prevent asthma by limiting oxidative damage [40]. The growing prevalence of asthma and the complications accompanying with disease management are the major priorities for the researchers [41], and the quest for natural anti-asthmatic components for supplementing the conventional therapy is ongoing. Dietary carotenoids, based on their structure and pharmacology, are anticipated to express favorable anti-asthmatic effects in the body for disease control [42]. An experiment lead by Hazelwood et al. displayed how lycopene supplementation improved allergic inflammation in a mouse model of Allergic airways disease (AAD). AAD was induced in BALB/c mice by intraperitoneal sensitization to lycopene supplement- or control-treated ovalbumin (OVA) and intranasal exposure. The degree of influence of the

supplementation on the infiltration of inflammatory cell into bronchoalveolar rinse fluid, goblet cell populations within the airways, blood and tissue of the lungs, regional lymph node ovalbumin (OVA)-specified release of cytokine, IgG1 levels in serum and performance of lungs in AAD were studied. Infiltration of eosinophil in bronchoalveolar rinse fluid, blood and tissue of the lungs and goblet cell counts within the airways, were decreased by supplementation. Additionally, lycopene supplementation reduced the Th2-associated cytokines IL-4 and IL-5 that were released in response to ovalbumin. These findings inferred that lycopene supplementation minimized allergic inflammation both in the lungs and blood vessels by reducing the action of Th2 cytokine. Therefore, lycopene supplementation might be used to prevent asthma [43]. In another experiment by Hwang et al., the protective effects of astaxanthin on asthma were tested using the OVA-induced mice model. In the test groups, 50 mg/mL astaxanthin was given orally, which suppressed the resistance, Newtonian resistance, flexibility, tissue elastance and tissue damping of the lungs. Moreover, astaxanthin inhibited the IL-4, IL-5 and total number of cells, while it escalated the IFN-γ in the BALF. Astaxanthin exposure decreased the overall IgG1, IgE and OVA-specific IgG1 and increased IgG2a and OVA-specific IgG2a in the sera. These findings astaxanthin possibly hold potential for curing asthma by the activation of Th1-mediated cytokine and inhibition of Th2-mediated cytokine (Table 1) [44].

Song et al. conducted a study to decide if lutein controls the inflammatory agents in murine asthma model induced with ovalbumin. Lutein administration notably inhibited the hyperresponsiveness of the airway caused by OVA-induced asthma. It also caused a remarkable mitigation of the invasion of inflammatory mediators into the bronchoalveolar washing. In addition, lutein weakened the Th2 response which was elevated in OVA-induced mice. These findings illustrate lutein as a powerful inhibitor which can lower the immunologic reactions of Th2 (Table 1) [45]. Another experiment by Zhu et al., reported that bixin protects mice against bronchial asthma though modulating PI3K/Akt pathway (Fig. 1). Bixin treatment ameliorates chronic airway inflammation and hyperresponsiveness, as well as prevents airway remodeling in a chronic asthmatic mouse model. In vitro experiments indicated that Bixin suppressed the epithelial mesenchymal transition induced by signaling of TGF-β. In addition, administration of Bixin also restored the steroids sensitivity in a mouse asthma model resistance to the glucocorticoids treatment [46].

3.2. Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are both serious medical diseases that can cause hypoxemia, diffuse infiltration on chest X-rays, hypercapnia, and significant loss in lung compliance. These are the symptoms of an inflammatory reaction of the lung that cause insults both directly and indirectly [47,48]. Mechanical ventilation is a crucial part of the treatment of ALI or ARDS, generally used to tackle the life-threatening hypoxia and hypercapnia caused by various underlying conditions like burns, aspiration, trauma, pneumonia, shock or sepsis [49,50]. But mechanical ventilation is responsible for causing serious harm to the lungs, observed in both clinical and experimental examination. The damage occurs due to barotrauma, periodic shutting and resuming of the alveoli and over-inflation. These conditions are together termed as "ventilator-associated lung damage"(VALI) [51,52]. VALI's actions can also activate inflammatory responses in lungs and blood circulation which ultimately bear the risk of causing dysfunction or failure of multiple organs or system [53].

Since there has been a long-term increase in the number of individuals suffering from lung injury, one of the primary goals of research is to identify bioactive molecules as potential therapeutic candidates for the treatment of ALI and ARDS. Crocetin, a natural apocarotenoid from crocus flower was observed to lower the expression of reactive oxygen species (ROS) and inflammatory components. Yang et al. examined the influence of crocetin on acute lung injury generated by lipopolysaccharide (LPS) in vivo (Fig. 2). The mice were pretreated with 50 and 100 mg/kg doses of Crocetin. It minimized the LPS-induced lung hydropsy and histological variations, maximized LPS-mediated function of superoxide dismutase (SOD) and reduced respiratory myeloperoxidase (MPO) activity. In addition, Crocetin treatment considerably lessened LPS-induced mRNA and expression of proteins which are important for MCP-1, IL-6 and TNF-α in lung tissue. Furthermore, the expression of phospho-IκB as well as the activity of NF-κB was decreased by crocetin in LPS-induced alteration of lung tissues. These outcomes direct that crocetin can protect mice against LPS-induced acute lung injury (Table 1) [54]. In another experimental study by Li et al., the influence of β-carotene to activate the JAK2/STAT3, NF-κB and MAPK signaling cascade was explored after introduction of LPS in cells of RAW264.7 and macrophages of the peritoneum. The findings depicted that β-carotene appreciably inhibited LPS-induced discharge of IL-6, IL-1β, TNF-α and their gene expression. LPS-triggered stimulation of JNK/p38 MAPK, IκB/NF-κB p65 and JAK2/STAT3 signaling pathway was considerably diminished by β-carotene while the extent of reduction depended on the dose (Fig. 2) So it can be decided that, LPS-mediated inflammation could be attenuated by β-carotene as it inhibits the JNK/p38 MAPK and NF-κB, JAK2/STAT3 signal transduction pathways in macrophages (Table 1) [55].

Wang X. et al., investigated whether allicin could reduce LPS-induced ALI in newborn rats and tried to discover the probable mechanism underlying it. Allicin notably lowered the concentration of TNF-α, interleukin-6 and malondialdehyde, and elevated the activity of superoxide dismutase in the bronchoalveolar lavage solution of LPS-administered rats. Moreover, by using western blotting and ELISA techniques, it was discovered that allicin administration escalated the synthesis of Bcl-2 protein and diminished the action of caspase-3/− 9 respectively, and elevated phosphorylated-Akt protein levels and phosphatidylinositol 3–kinase (PI3K) in neonatal rats with LPS-induced ALI (Table 1). The outcomes of the study proposed that allicin cure LPS-induced ALI in neonatal rats by relieving inflammation, oxidative stress and apoptosis via the PI3K/Akt signaling pathway. Thus it may be used for progression of a new drug for treating ALI [56].

3.3. Chronic obstructive pulmonary disease (emphysema and chronic bronchitis)

COPD is an inflammatory condition that obstructs the airways and airflow limits of the lungs, thus it becomes troublesome to breathe freely [57]. COPD is one of the leading global health problems responsible for a significant portion of the chronic morbidity and mortality worldwide. It is the fourth major cause of mortality worldwide and its prevalence and mortality can be expected to rise further [58]. From the Global Initiative for Chronic Obstructive Lung Disease, we came to know that in 2012, around three million patients lost their lives due to COPD, which was 6% of total deaths globally [59]. COPD is primarily caused by biological modulators like inflammation and oxidative stress which are caused by free radicals, released as a result of smoking and lack of antioxidant-rich foods in regular diet [60,61]. Emphysema and chronic bronchitis are the two main kinds of COPD that can be distinguished. Emphysema is an accelerating lung condition due to which the lung tissue degrades slowly, the alveoli in particular (tiny air sacs). Eventually, the air sacs burst due to the damage and a single large air pocket is formed, replacing the multiple small alveoli. As a result, the injured lung tissue has a smaller surface area, which restricts air, which prevents oxygen from passing through the circulation. Additionally, the obstruction gradually overfills the lungs, making breathing difficult [62]. However, current experimental findings affirmed that dietary carotenoids exhibit good treatment opportunities for lung emphysema patients. For reference, a study denoted that β-cryptoxanthin reversed nicotine-affected lung SIRT1 to normal range and suppressed nicotine-induced

Table 1
Preclinical experimental findings on the use of dietary carotenoids in respiratory diseases.

Respiratory Diseases	Compound	Study model	Doses/Conc.	Results	References
Acute lung injury and Acute respiratory distress syndrome	Crocetin	In vivo (male and female ICR mice)	50 and 100 mg/kg	Crocetin suppressed the NF-κB pathway, which decreased lipopolysaccharide-induced acute lung damage (ALI).	[54]
	Crocin	In vivo (male BALB/C mice)	50 mg/kg	Crocin effectively protected against LPS-induced ALI, and the protective actions of crocin may be due in part to iNOS inhibition.	[108]
	Lutein	In vivo (male Swiss albino mice)	40 and 100 mg/ kg	Lutein inhibits the ROS/NF-kB/MAPK pathway, which can help to alleviate CP-induced pulmonary damage.	[109]
	Fucoxanthin	In vitro (RAW264.7 cells)	0–20 μM	LPS-induced upregulation of pro-inflammatory cytokines (IL-1, IL-6, iNOS, COX-2, and TNF-α) was reduced by fucoxanthin via the AMPK/ NF-κB signalling pathway.	[110]
	β-carotene	In vitro (RAW264.7 cells)	50, 75 and 100 μM	In macrophages, β-carotene reduced LPS-induced inflammation by inhibiting the NF-κB, JAK2/STAT3, and JNK/p38 MAPK signalling pathways.	[55]
	Allicin	In vivo (male Sprague-Dawley neonatal rats)	80 mg/kg	Through the PI3K/Akt pathway, allicin reduced LPS-induced ALI in born rats by reducing oxidative stress, inflammation, and apoptosis.	[56]
	Lycopene	In vivo (male BALB/c mice)	100 mg/kg	Lycopene demonstrated protective effects on an LPS-induced mouse model of ALI	[111]
		In vivo (male and female ICR mice)	80 mg/kg	Lycopene attenuated oleic acid-induced ALI	[112]
	Astaxanthin	In vivo (C57BL/6 J mice)	100 mg/kg	Astaxanthin prevented against lipopolysaccharide-induced acute lung injury and sepsis by blocking activation of the MAPK/NF-κB signalling pathway	[113]
		In vivo (C57BL/6 J mice)	60 mg/kg/ day	Astaxanthin protected ALI in mice, and the mechanism behind this protection could be related to reduced NF-κB P65 expression and inflammatory response	[114]
		In vitro (RAW264.7 cells)	20 mg/kg	Astaxanthin inhibited the TLR4/MyD88 signalling pathway and attenuated LPS-increased inflammatory factors in vitro	[115]
		In vivo (C57 mice)	100 mg/kg	ASTA reduced lung inflammation and oxidative damage in mice induced by OTA exposure through the Nrf2 signalling pathway	[116]
Asthma	Bixin	In vivo (female BALB/c mice)	50 mg/kg or 100 mg/ kg	Bixin suppressed allergic airway inflammation and reversed glucocorticoids resistance, as well as alleviated airway remodelling and airway hyperresponsiveness (AHR) in asthmatic mice	[46]
	Crocetin	In vivo (C57BL/6 J mice)	100 μmol/L	Crocetin treatment significantly reduced the severity of an ovalbumin (OVA)-induced asthma in mice and significantly increased the levels of TIPE2 and Foxp3 in Treg cells and the number of Treg cells	[117]
	All-trans retinoic acid	In vivo (female BALB/c mice)	400 μg/ mouse	Attenuated airway inflammation by inhibiting Th2 and Th17 response in experimental allergic asthma	[118]
	Lutein	In vivo (female BALB/c mice)	10 mg/kg	Lutein regulated inflammatory mediators in OVA-induced murine asthma model	[45]
	Lycopene	In vivo (male BALB/c mice)	8 mg/kg	Lycopene supplementation reduced allergic inflammation in the lungs and systemically, by decreasing Th2 cytokine responses; thus, showed protective effect against asthma	[43]
		In vivo (rats)	10 and 20 mg/kg/day	Lycopene were effective in the treatment of allergic rhinitis, asthma, etc. and this effect was found to be stronger with increasing doses of lycopene	[119]
	Carotene	In vivo (rats)	30 mg/kg	Carotene exhibited potential benefits for consumption as nutritional adjuncts in asthmatic disease	[120]
	Fucoxanthin	In vivo (female BALB/c mice)	10 mg/kg or 30 mg	Fucoxanthin suppressed the synthesis of pro-inflammatory cytokines, eotaxin, and reactive oxygen species in BEAS-2B cells and lowered monocyte cell adhesion to the cells	[121]
	Astaxanthin	In vivo (female C57BL/ 6 mice)	50 mg/kg	Astaxanthin demonstrated therapeutic potential to treat asthma via inhibiting Th2-mediated cytokine and enhancing Th1-mediated cytokine	[44]
		In vivo (male Hartley guinea-pigs)	10 mg/kg	Astaxanthin significantly reduced asthma-associated inflammation in asthmatic guinea pigs	[122]
Chronic obstructive pulmonary disease	β-cryptoxanthin	In vivo (male A/J mice)	10 and 20 mg/kg/day	β-cryptoxanthin supplementation at two different doses was associated with reductions of the nicotine-promoted emphysema in mice treated with nicotine	[63]
	Lycopene	In vivo (ferrets)	2.2 or 6.6 mg/kg BW/ day	Lycopene demonstrated protective effects against NNK/CS induced COPD which is associated with maintaining a pulmonary cholesterol homeostasis, through the regulation of the impaired reverse cholesterol transport	[64]
		In vivo (male C57BL/6 mice)	25 or 50 mg/ kg/day	Lycopene repaired lung damage in emphysema caused by cigarette smoke exposure via decreasing the levels of TNF-α, IFN-γ and IL-10	[67]
		In vitro (SAMP1 mice strain)	5 mg	Lycopene abundantly prevents SAMP1 mice from the development of smoke-induced emphysema	[68]
	Astaxanthin	In vivo (male BALB/c mice)	50 mg/kg	Astaxanthin protected against oxidative stress via Nrf2 and ameliorates cigarette smoke-induced emphysema	[64]
		In vivo (male C57BL/6 mice)	0.02%(w/w)	Astaxanthin suppressed cigarette smoke-induced emphysema through Nrf2 activation in mice	[123]
		In vitro (RAW264.7 macrophages)	10 and 20 mg/kg	Astaxanthin showed therapeutic and prophylactic potential in the airway inflammatory response associated with COPD	[124]
Lung cancers	Alpha carotene	In vivo (C57BL/6 male mice)	2.5 μg	Alpha carotene decreased matrix metalloproteinase (MMP)− 2, − 9, and urokinase plasminogen activator invasion, migration, and activity,	[80]

(*continued on next page*)

Table 1 (*continued*)

Respiratory Diseases	Compound	Study model	Doses/Conc.	Results	References
				but enhanced tissue inhibitor of MMP (TIMP)− 1, − 2 protein production	
	Lutein	In vitro (A549 cells)	0–50 μM	Lutein suppresses the PI3K/AKT signalling pathway and causes apoptosis	[81]
	Lycopene	In vivo (C57BL/6 mice)	6 mg/kg	Lycopene prevents tumorigenesis	[82]
		In vitro (A549 cells)	0–10 μM	Lycopene plays a role in tumorigenesis suppression via a variety of mechanisms, including suppressing NF-κB	[125]
		In vitro (A549 and HeLa cells)	10 mmol/l	Lycopenoic acid which is the active metabolite of lycopene may be used as a chemopreventive drug in the fight against lung cancer	[126]
	Astaxanthin	In vitro (A549 and H1703)	2.5–20 μM	In non-small cell lung cancer cells, astaxanthin produced synergistic cytotoxicity and cell growth suppression, as well as lower levels of phospho-AKT (Ser473) and Rad51 expression	[83]
		In vitro (H1650 or H1703 cells)	20 μM	Astaxanthin inhibits MKK1/2-ERK1/2-mediated TS expression, which is a key regulator in increasing pemetrexed-induced cytotoxicity in NSCLC cells	[127]
		In vivo (C57BL/6 J female mice)	100 mg/kg	Macrophages and neutrophils were reduced in BALF, while lymphocytes were unchanged	[124]
Pulmonary fibrosis	Lutein	In vivo (C57BL/6 J female mice)	100 and 200 mg/kg	Lutein has a protective impact against pulmonary fibrosis by decreasing inflammation, oxidative stress, and increasing antioxidant potential	[87]
	Lycopene	In vivo (rats)	4 mg/mL	Lycopene lowering of plasma TNF-α and NO levels, as well as the down-regulation of TNF-α in the lungs, all contribute to the alleviation of pulmonary fibrosis	[88]
	Crocin	In vivo (rats)	20 mg/kg	Crocin has anti-inflammatory benefits; down-regulation of TLR4, IL-10 expression, and ultimately, down-regulation of tissue expression of TNF-α and TGF-1β is the major route engaged in the documented anti-fibrotic actions	[89]
		In vivo (rats)	20 mg/kg	Crocin suppressed the bleomycin-induced decreases in catalase, superoxide dismutase, and tPA mRNA levels while enhancing PAI-1 mRNA expression	[128]
	Astaxanthin	In vivo (C57BL/6 J female mice)	5 mg/kg	To reduce pulmonary fibrogenesis, astaxanthin inhibits activated fibroblast proliferation and migration, and mitochondria-mediated signal pathways	[90]
		In vivo (C57BL/6 J female mice)	50 mg/kg	Astaxanthin successfully inhibited AHR, inflammatory cell infiltration in the lungs, mucus hypersecretion, lung fibrosis, and caspase-1 and caspase-3 expression	[44]
		In vitro (A549 and MRC-5 cells)	30 and 40 μM	Astaxanthin prevents pulmonary fibrosis from progressing by blocking transdifferentiation, reducing proliferation, and inducing apoptotic in activated cells	[91]

tumorigenesis and emphysema in the lungs of A/J mice [63]. β-cryptoxanthin supplement reinstalled the nicotine-inhibited production of lung SIRT1, RAR-β and p53 compared to that of the reference group, escalated the probability of survival, and diminished the phosphorylation of AKT and amount of lung IL-6 mRNA (Fig. 3). The outcomes of the experiment showed that β-cryptoxanthin is a prophylactic substance against emphysema and SIRT1 is a likely target [63]. Rakic et al., noted that lycopene antagonized tobacco-induced COPD by regulating reverse cholesterol shift in ferrets. Results displayed that, at an elevated dose, dietary lycopene considerably reduced emphysema, NNK/CS-generated chronic bronchitis, and preneoplastic lesions, considering squamous metaplasia and asymptomatic adenomatous hyperplasia, when contrasted with the NNK/CS control [64]. Crocin (50 mg/kg) also assisted mice with cigarette-induced COPD by inhibiting inflammatory pathways mediated by PI3K/Akt. Crocin therapy lessened the number of lymphocytes, neutrophils, macrophages and other such inflammatory cells. Crocin also decreased the penetration of peribronchial inflammatory cells and the concentration of proinflammatory cytokines like TNF-α, IL-6, and IL-1β in lung tissue and BALF. The effect of Crocin on stimulation of the NF-κB pathway caused by cigarette smoke was also overridden by insulin-like growth factor 1, a PI3K activator (Table 1) [65].

The anti-inflammatory and antioxidant activity of nutritional supplement of lycopene was researched in two in vivo experiments using mice models to find out if it is beneficial for emphysema caused by chronic exposure to cigarette smoke. Lycopene was administered at 25 mg/kg and 50 mg/kg body weight in C57BL/6 mice. After 60 days of treatment, the harmful reactions of long-term cigarette smoke in patients consuming 12 cigarettes/day was reduced [66,67]. Both of the doses of lycopene decreased lipid peroxidation, DNA destruction and increased redox equilibrium. The therapy also elevated the actions of SOD, glutathione (GSH) and catalase (CAT) and lowered the levels of TNF-α, interferon-gamma (IFNγ) and IL-10. However, neither of the doses was able to successfully stop the weight loss caused on by long-term cigarette usage. A previous research conducted by the same researchers, where 25 and 50 mg/kg BW/day doses of lycopene were given after only five days of cigarette exposure, not long enough to produce emphysema, noted that lycopene therapy diminished the activation of neutrophil and entry of macrophage into the BALF, and also lowered IL-10, IFNγ and TNF-α levels (Table 1 and Fig. 3) [66,67]. In another in vivo experimentation, senescence-accelerated mouse (SAM) model was used to estimate the relation between age-dependent progressions of emphysema and examine the effect of lycopene supplement on the development of emphysema. For this, the mice were exposed to cigarette smoke for 30 min per day, five days per week, for eight weeks to mimic senile lung and then tomato juice carrying 5 mg of lycopene was administered which showed repressing effect on the formation of cigarette smoke-induced emphysema. It appeared that dietary lycopene supplementation have beneficial impact on cigarette smoke-induced bronchiolitis, chronic obstructive lung disease, and emphysema [68].

3.4. Lung cancer

Lung cancer is a major type of carcinoma, formed in tissues of the lungs, generally inside the cells lining the air passages. It is the leading type of cancer responsible for majority of the cancer mortality in men and women worldwide [69]. Primary lung cancer is classified into two types according to the nature of cells in which the cancer develops [70]. The most recurrent lung cancer type is non-small-cell lung cancer or

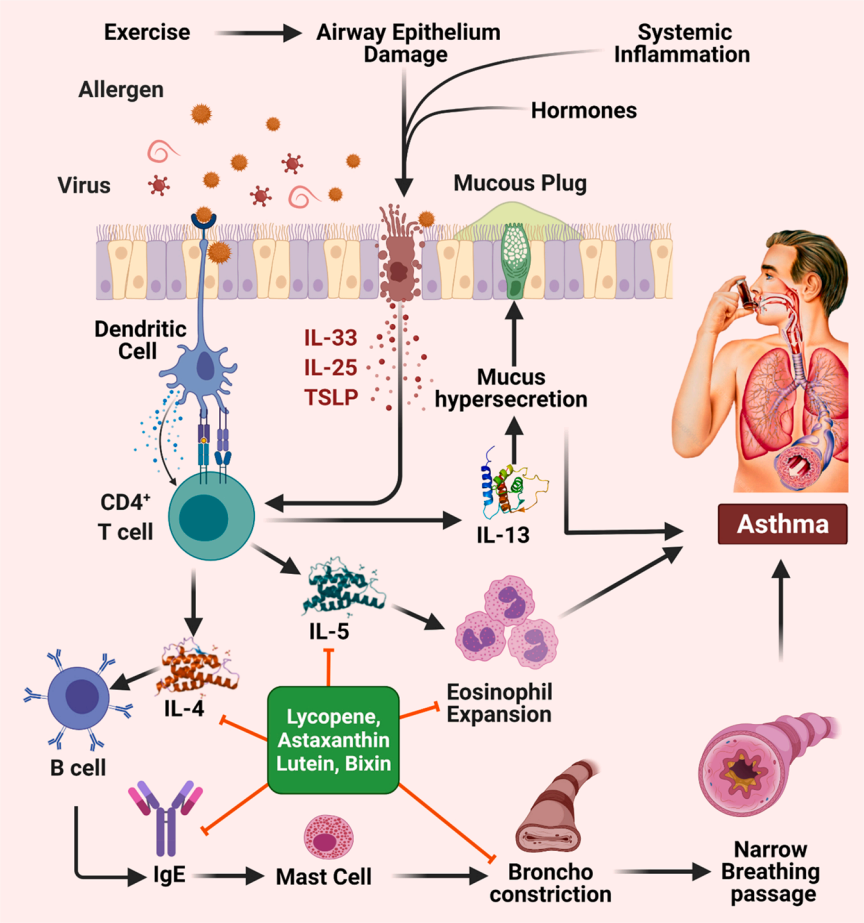

Fig. 1. Effects of dietary carotenoids against asthma.

NSCLC consisting about 87% cases. Three types of NSCLC are-squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma [71,72]. The second type of lung cancer is small-cell lung cancer which is less frequent but advance more rapidly than NSCLC [73]. Though lung cancer can attack anybody, there are numerous risk factors that multiply the possibilities of developing it, among which the most prominent one is smoking [74]. It is blameworthy for nearly 9 out of 10 and 8 out of 10 cases of lung cancer in men and women respectively (Table 1) [75]. In general, there are no signs or symptoms present in the primary stages of lung cancer but in later stages, symptoms such as: chronic coughing, trouble breathing, hemoptysis, emaciation, coughing headaches and inexplicable fatigue are observed [76].

The number of lung cancer patients are increasing to a substantial amount and is predicted to be almost 20 million by 2030 [77,78]. As a result, the main goal of cancer research is to identify controllable oncogenic alterations related to the emergence of cancer. Several cancer biomarkers have been linked to carotenoids, it has been suggested [79]. The anti-metastatic action of α-carotene against Lewis lung carcinoma (LLC) was demonstrated in an experiment using LLC-xenografted C57BL/6 mice in combination with taxol. Examination of the cell cultures unveiled that α-carotene effectively suppressed invasion, relocation and actions of matrix metalloproteinase-2 (MMP-2), MMP-9 and urokinase-type plasminogen activator (uPA) but elevated the expression of plasminogen activator inhibitor-1 (PAI-1), tissue inhibitor of MMP-1 (TIMP-1), and TIMP − 2 proteins (Fig. 4). Results from the mice model disclosed that lung metastasis was impressively lessened by α-carotene intake (5 mg/kg) while primary tumor growth was not affected. Moreover, α-carotene treatment appreciably reduced expression of integrin β1 protein but enhanced expression of TIMP-1 and PAI-1 protein without changing expression of TIMP-2 protein and phosphorylation of focal adhesion kinase (FAK) protein in respiratory tissues. Altogether, α-carotene significantly slows down LLC metastasis and lung metastasis in LLC-induced mice [80]. Another research revealed that lutein hinders cell growth and stimulates apoptosis using the PI3K/AKT/mTOR signaling route in A549 human non-small-cell type lung cancer cells [81]. To establish the molecular mechanism manifested by lutein to instigate apoptosis in A549, a double-staining procedure was performed utilizing TUNEL and DAPI smearing assays. The results showed that lutein controls the phosphoinositide 3-kinase PI3K/AKT signaling molecules, which are occasionally deregulated in cancerous state, and induces apoptosis in A549, suggesting that it may work as a potent natural anticancer drug against lung cancer with few side effects [81].

Jiang et al. explored to see if lycopene could aid the impact of anti-PD-1 therapy on lung cancer. Lycopene helped anti-PD-1 to increase the amount of IFN-γ and IL-1 while decrease the concentration of IL-10 and IL-4 in the spleen of LLC-injected mice. The CD4 + /CD8 + ratio was raised in the spleen and IFN-γ-expressing CD8 + T cells were elevated in tumor tissues due to lycopene therapy. It reduced PD-L1 expression by triggering JAK and suppressing phosphorylation of AKT upon activation of IFN-γ. These results suggested that lycopene could be turned into a promising ancillary drug to ameliorate the efficiency of anti-PD-1 therapy by synergistic action (Fig. 4) [82]. Another examination by Ko et al. discovered that astaxanthin can cause down-regulation of Rad51 expression by inactivating AKT kinase to intensify cytotoxicity generated by mitomycin C in NSCLC cells of human [83]. Astaxanthin treatment obstructed the viability and expansion of two NSCLC cells, namely H1703 and A549. It lowered the expression of Rad51 and protein level of

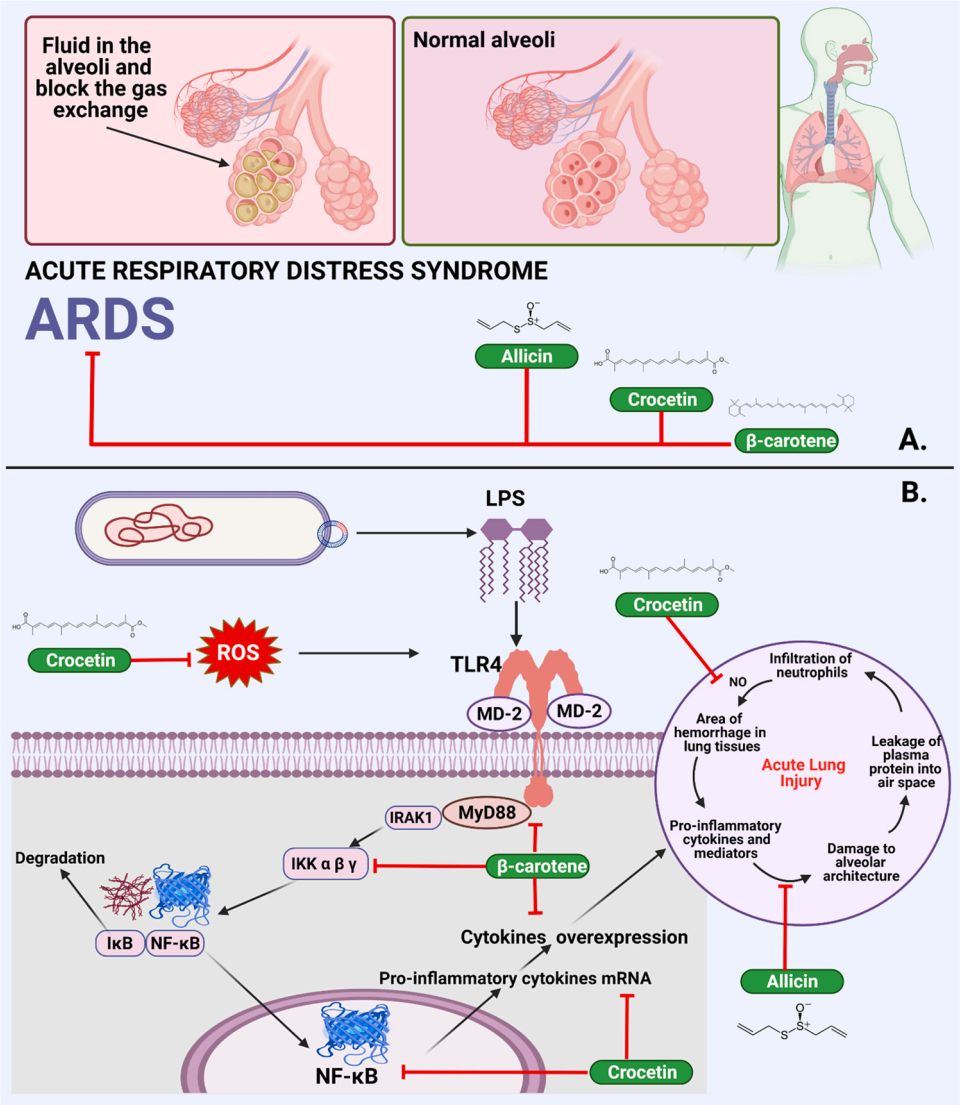

Fig. 2. Effects of dietary carotenoids against Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

phospho-AKT (Ser473) in a dose and time-dependent style. In addition, constantly active AKT (AKT-CA) vector expression redeemed the minimized level of Rad51 mRNA and protein in non-small cell lung cancer cells treated with astaxanthin (Table 1) [83].

3.5. Pulmonary fibrosis

Pulmonary fibrosis is a persistent and progressive and most routinely diagnosed interstitial lung disease (ILD), that arises from an atypical mechanism of wound recovery in tissues of the alveoli as a feedback to repetitive lung damage in genetically vulnerable population [84]. Some factors that contribute to the progression of pulmonary fibrosis have been discovered, despite the fact that the etiology of the disorder is not fully understood. Such as- alveolar injury, infection, pollution, aspiration, dust and fibers [85]. The prognostication of pulmonary fibrosis is quite insufficient. Currently there are only two anti-fibrotic agents, nintedanib and pirfenidone which are approved by the FDA for minimizing symptoms of the disease (Table 1) [86].

Dietary carotenoids have gained support as a potential therapy for pulmonary fibrosis. Utilizing a mouse model in which lung fibrosis was induced with bleomycin, researchers investigated the anti-fibrotic efficacy of lutein. Administration of 100 and 200 mg/kg dose of lutein blocked the weight reduction and mortality caused by bleomycin. It also weakened bleomycin affected rise of total cell count, differential cell count and myeloperoxidase, inflammatory cell incorporation in pulmonary tissue. Likewise, lutein treatment reinstated action of superoxide dismutase decreased by bleomycin introduction. The cumulative findings showed that lutein has anti-inflammatory, anti-oxidative, and anti-oxidative stress capabilities that may be useful in the fight against pulmonary fibrosis (Fig. 5) [87]. Another trial disclosed that lycopene present in tomatoes partly cures the pulmonary fibrosis generated using bleomycin in test rats. The inhibition of TNF-α, oxidative stress and nitric oxide (NO) levels in plasma and the decrease in receptors for TNF-α in lung cells play a part in the mitigation of PF in rats treated with lycopene [88].

Zaghloul et al. examined the significant anti-fibrotic, antioxidant and anti-inflammatory potentials of crocin to counter pulmonary fibrosis caused by BLM. Crocin promisingly lowered BLM-affected lung damage and its impact was equivalent to the established anti-fibrotic agent halofuginone. The anti-fibrotic, anti-inflammatory and antioxidant activities noticed are assumed to be the curative action of crocin. The major mechanism of the anti-inflammatory actions seen is the down-regulation of IL-10 and TLR4 expression. Anti-fibrotic activities result due to down-regulation of TGF-β1 and TNF-α tissue expression, and antioxidant effect is caused by the deformation of HO-1 and Nrf2 pathways [89]. Astaxanthin also prolonged noncoding RNA, enervated

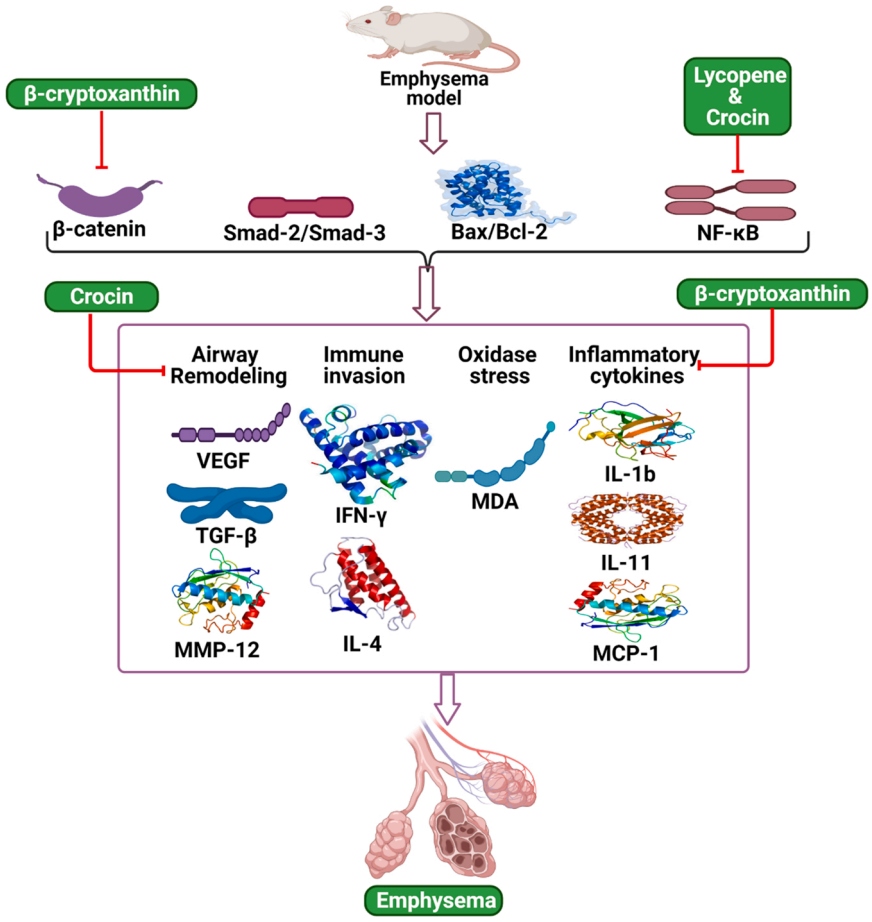

Fig. 3. Effects of dietary carotenoids against emphysema.

pulmonary fibrosis through mitochondria-induced signaling pathways, and inhibited fibroblast proliferation and migration [90]. Astaxanthin also relieved lung fibrosis both in vitro and in vivo by obstructing proliferation, averting lineage reprogramming, and encouraging apoptosis of stimulated cells. It hampered the propagation of activated MRC-5 and A549 cells at average repressing levels of 30 and 40 μM, respectively. To conclude, astaxanthin could partly block the propagation of pulmonary fibrosis and mitigate the symptoms by stopping transdifferentiation, repressing multiplication and triggering programmed death of activated cells [91].

4. Clinical status

Carotenoids are fat-soluble pigments present in fruits and vegetables that give them their bright colours of yellow, orange, red, and green. Carotenoids such as β-carotene, β-cryptoxanthin, zeaxanthin, lycopene, and lutein are abundant in human blood, accounting for nearly 90% of the entire plasma pool of carotenoids. Increased plasma carotenoid levels may boost immune response and reduce the risk of infectious illnesses. Acute respiratory infections are the most common type of infectious diseases [92].

One of the best indicators of fruit and vegetable consumption is serum carotenoid levels. The primary serum carotenoids and the food intake they usually constitute are α-carotene and β-carotene (oranges, carrots and green leafy vegetables), zeaxanthin and lutein (corn and green leafy vegetables), and β-cryptoxanthin (citrus and watermelon), and lycopene (tomato) [93]. In a study of healthy people aged 35–79 years without respiratory disease in western New York State, only β-cryptoxanthin, and no other carotenoids, was independently associated with lung function [94].

There has not been much research on the association between serum carotenoids and lung function in older and more impaired populations. The people receiving significant dosages of β-carotene supplementation were found to have an increased lung cancer risk in two large preventive trials in high-risk populations. Despite these dismal results, blood β-carotene at baseline was positively linked with lung function in one of these studies, and β-carotene intake was positively associated with pulmonary function in a cross-sectional investigation. It is unclear whether the observed link between β-carotene consumption and pulmonary function is caused by β-carotene alone or additional carotenoids and nutrients connected with β-carotene intake, according to a number of theories that have been put out to explain this discrepancy [95]. More than 600 carotenoids have been identified to date, with many of them (such as β-cryptoxanthin, lutein/zeaxanthin, β-carotene, and lycopene) having high antioxidant properties [96,97].

Among the carotenoids, β-cryptoxanthin is the carotenoid most associated with lung function, followed by lutein and zeaxanthin. When analysed individually, β-carotene, β-cryptoxanthin, lutein/zeaxanthin and retinol were favourable inter-related with forced expiratory volume (FEV), whereas β-cryptoxanthin, lutein/zeaxanthin, and β-carotene were positively related to force vital capacity (FVC). However, when all of the serum parameters were taken into account, β-cryptoxanthin was found to have strongest relationship with both FEV and FVC. In addition to β-cryptoxanthin, only retinol and lutein/zeaxanthin showed independent effects on FEV (retinol) and FVC (lutein/zeaxanthin) [93,98]. Because consumption of high-carotene foods is linked to other lifestyle choices that may influence lung function, studies concentrating on dietary intake raise questions about the true nature of the link between these carotenoids and lung function. [99,100]. Thus, measuring carotenoids levels in the blood has been suggested as a way to investigate this

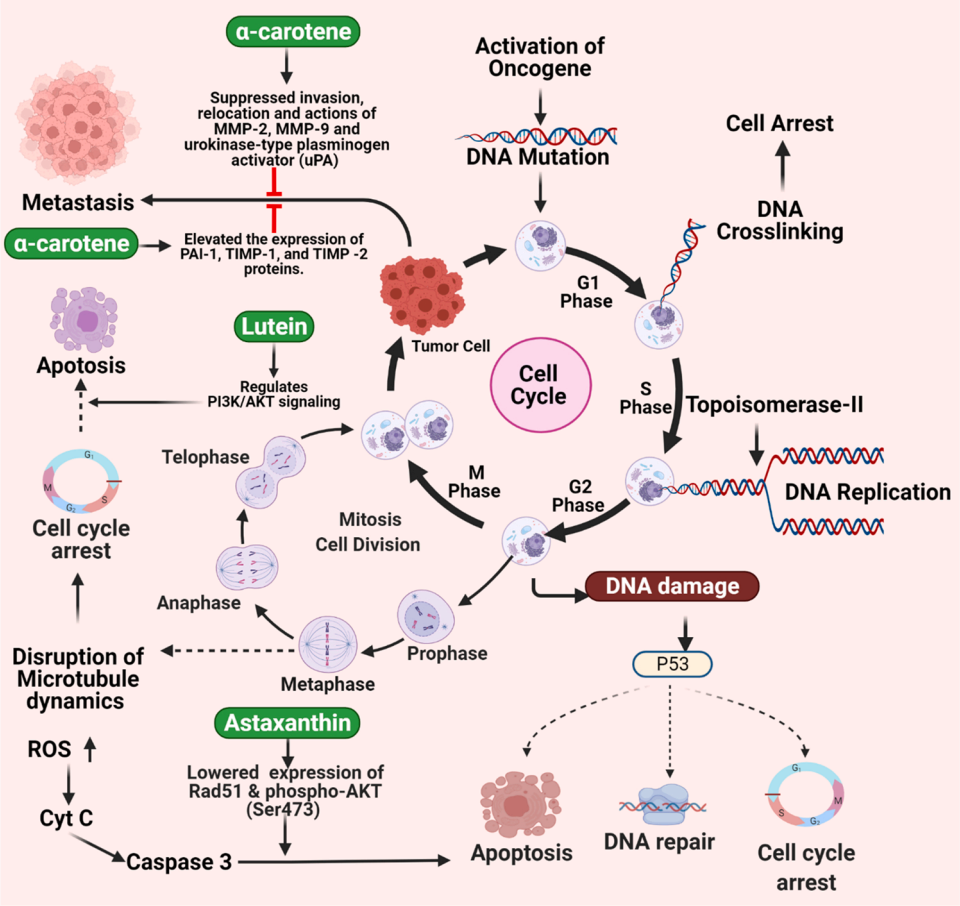

Fig. 4. Effects of dietary carotenoids against lung cancer.

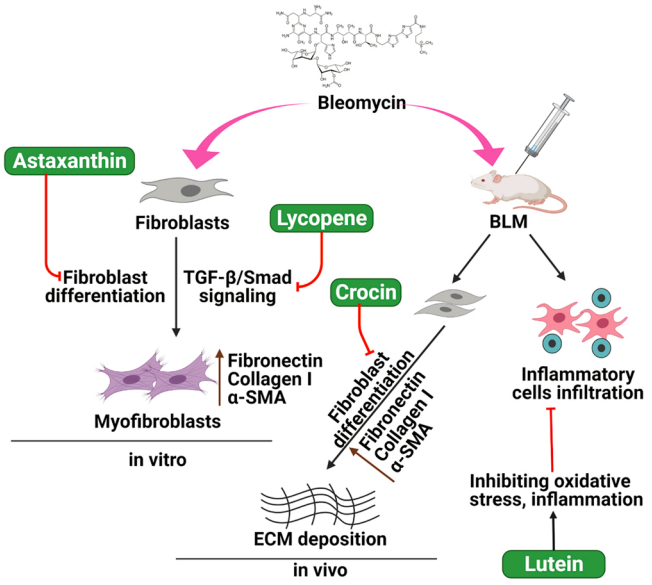

Fig. 5. Effects of dietary carotenoids against pulmonary fibrosis.

link. In epidemiologic investigations, the interrelationship of serum carotenoids and their correlation with pulmonary function has not been explored concurrently. Few epidemiologic studies have looked at blood carotenoids and lung function, and just one research, conducted in a group of older Dutch people, assessed several antioxidant carotenoids (Table 2). The strongest links to lung function were found in this study for α-carotene, β-carotene, and lycopene, however serum levels of α-carotene and lycopene were lower than in the United States [20].

5. Safety and toxicity of carotenoids

Carotenoids can be obtained from both fore milk and hind milk of mothers, and they are extensively dispersed in the human diet. The US FDA (Food and Drug Administration) has repeatedly approved supplement manufacturers 'Generally Recognized As Safe' labels for a variety of carotenoid-rich products, including palm oil carotenoids, lutein-, zeaxanthin-, and lycopene-containing products, some of which are tomato-based and also contain the colorless carotenoids phytoene and phytofluene. [99,101].

Dietary carotenoids, in particular, are safe at amounts substantially higher than those observed in people who eat a conventional diet. As a result, the EFSA (European Food Safety Authority) has issued instructions for safety limits of daily consumption of some carotenoids, mentioned in some circumstances as appropriate daily intakes (ADI) [100]. For example, the ADI for lutein obtained from flower extract of *Tagetes erecta* used as an additive is calculated to be 1 mg/kg/day, while that for lycopene is 0.5 mg/kg/day [102]. Although no ADIs for mixed carotenes and/or β-carotene have been defined, it is regarded safe to consume them as additives at amounts less than 15 mg/kg/day [103]. Intakes of 0.75 mg/kg/day of zeaxanthin (as a food supplement ingredient) do not cause any deleterious effects to health. The EFSA has set an ADI of 0.3 mg/kg/day for β-apo-8-carotenal, one of the apocarotenoids. When used as a food additive, annatto includes the apocarotenoids, namely bixin (6 mg/kg/day) and lower levels of norbixin (0.3 mg/kg/day) as ADIs respectively [100,104]. Given these findings, it is obvious that consuming significant amounts of carotenoids (far higher

Table 2
Clinical findings on the use of dietary carotenoids in patients with respiratory diseases.

Respiratory Diseases	Compound	Study model	Doses/Conc.	Results	References
Lung infections / Chronic obstructive pulmonary disease (COPD)/ Acute lung injury and Acute respiratory distress syndrome	Serum α-carotene, β-carotene	1002 women, aged 65 years and older	–	Positive association between higher serum α-carotene and β-carotene concentrations and FEV1 and FVC (all $p < 0.05$) in separate multivariate linear regression models	[95]
	Serum carotenoids (α-carotene, β-carotene, lycopene, β-cryptoxanthin, zeaxanthin, and lutein), α-tocopherol	noninstitutionalized Dutch, elderly age 65–85 years (n = 5528)	–	Particularly α-carotene, β-carotene, and lycopene were positively associated with lung function in the elderly	[20]
	Lycopene	15 clinically stable COPD patients and 15 healthy non-smoker control	20 mg/day	Significant increases in mean SOD, and CAT levels ($p < 0.001$), and significant decreases in mean MDA, IL-6, IL-b, and TNF-a levels ($p = 0.001$, $p < 0.001$, $p = 0.002$, $p < 0.001$, respectively) were observed	[129]
	β-cryptoxanthin	22 smokers, if they had smoked more than 100 cigarettes in their lifetime -veterans	–	Correlation between dietary β-cryptoxanthin and the high serum level of this compound with the decreased rates of COPD were observed	[130]
	α-tocopherol and β-carotene	29,133 participants	50 mg/day and 20 mg/day	Results indicate no benefit from supplementation with α-tocopherol or β-carotene on the symptoms of COPD	[131]
Asthma	Serum carotenoids (β-carotene, lycopene, β-cryptoxanthin, zeaxanthin, and lutein)	General population sample (aged 35–79 years) from Erie and Niagara Counties (New York), recruited as part of an ongoing series of population-based case-control studies (n = 2409)	–	Correlation between dietary β-carotene and β-cryptoxanthin and the high serum level of this compound with the decreased rates of asthma were observed	[93]
	Serum carotenoids (β-carotene, lycopene, β-cryptoxanthin, zeaxanthin, and lutein)	School children (aged 4–18 years) in Ongkaluck district of Thailand, during November and December 2010 (n = 423)	–	There was no significant difference in dietary intake of carotenoids and skin carotenoid level between asthmatic and non-asthmatic children. Skin carotenoid level significantly correlated with dietary carotenoids intake. Carotenoids' intake and skin carotenoid levels were found to be not associated with the risk of asthma in Thai children.	[132]
	Serum carotenoids (β-carotene, lycopene, β-cryptoxanthin, zeaxanthin, and lutein)	Adults with stable asthma (n = 15) and healthy controls (n = 16)	–	Compared to healthy controls, subjects with asthma had lower whole blood levels of total carotenoids, β-cryptoxanthin, lycopene, lutein, α-carotene and β-carotene compared to healthy controls. Whole blood, but not plasma or sputum, carotenoid levels are deficient in asthma. Plasma carotenoid levels reflect airway carotenoid levels and when plasma levels are improved using oral supplements this is reflected in the airway	[133]
	Lycopene	Asthmatic adults (n = 137)	45 mg/day for 14 weeks	Improved clinical asthma outcomes by suppressing airway inflammation	[134]
	Lycopene	Asthmatic adults (n = 32)	45 mg/day for 10 days	Suppression of airway inflammation improved clinical asthma results.	[135]
	Lycopene	Asthmatic adults (n = 20)	30 mg/day for 7 days	Lycopene has a preventive effect against exercise-induced asthma when taken on a daily basis.	[136]
Tuberculosis	Lutein + Zeaxanthin, β-cryptoxanthin, total lycopene, α-carotene, and total β-carotene)	180 case patients with viable samples and 709 matched controls	–	Vitamin A supplementation among individuals at high risk of tuberculosis may provide an effective means of preventing tuberculosis disease.	[137]
Cancers	β-carotene	29,133 males aged 50–69 years old, who were heavy cigarette smokers	20 mg/day	Unexpectedly participants receiving β-carotene (alone or in combination with vitamin E) had a significantly higher incidence of lung cancer and total mortality.	[138]
	β-carotene	18,314 asbestos workers and smokers	30 mg/day + 25,000 L Uretinol/day	Overall lung cancer incidence was increased by 28% in the supplemented subjects and total mortality was also increased	[139]
	β-carotene	22,071 males			[140]

(*continued on next page*)

Table 2 (*continued*)

Respiratory Diseases	Compound	Study model	Doses/Conc.	Results	References
			50 mg every other day)	there was no significant effect-positive or negative-of 12 years of supplementation of beta-carotene on cancer	
	β-carotene	25,802 adults	–	28 individuals developed oral or pharyngeal cancer. Serum analyses indicated that prediagnostic serum levels of all the major individual carotenoids, and particularly β-carotene, were lower among the case group than among controls selected from the same cohort	[141]
	β-carotene	18,314 smokers, former smokers, and workers exposed to asbestos	30 mg of β-carotene per day	There were 388 new cases of lung cancer, yielding a relative risk of such cancer of 1.28 among the subjects who received beta carotene and retinyl palmitate, as compared with those who received placebo.	[142]
	β-carotene	22,071 male physicians, aged 40–84 years of age	50 mg on alternate days	No significant differences in the number of cases of lung cancer (82 in the beta carotene group vs. 88 in the placebo group)	[139]
	β-carotene and lycopene	35 lung cancer patients and 33 healthy people	–	This study is the first comparison between dietary intake of carotenoids and their serum concentrations in participants with and without lung cancer. In spite of a higher dietary intake of β-carotene and lycopene (as their dietary sources, fruits and vegetables) by lung cancer patients, serum concentration of β-carotene and lycopene were significantly lower than those without lung cancer. This condition probably is caused by an increased oxidative stress, lower absorption and bioavailability of carotenoids, and/or any probable isomeric change of carotenoids in the body of lung cancer patients due to an increased oxidative stress.	[143]

than usual dietary intakes) is safe (Table 3).

Due to unexpected mixed-negative results from two large trials that evaluated the notion that -carotene lowers cancer risk, the use of dietary supplements in carotenoids research has been thoroughly reevaluated. According to the cancer prophylaxis research, α-tocopherol, β-carotene (ATBC), supplementing smokers with α-tocopherol, β-carotene, or both for 5–8 years should minimize the risk of lung cancer and other cancers. A total of 30000 Finnish men smokers aged 50–69 were randomly assigned to one of four groups: α-tocopherol (50 mg/day), β-carotene (20 mg/day), α-tocopherol+ β-carotene, or placebo. There was no reduction in the incidence of lung cancer among the males who got α-tocopherol, and there was no proof of an interconnection between α-tocopherol, and β-carotene in terms of the risk of such malignancy. Surprisingly, men who received β-carotene had a greater rate of lung cancer than men who did not [105].

Concurrently, the Carotene and Retinol Efficacy Trial (CARET), which included 18,000 smokers, former smokers, and asbestos workers, studied the effects of supplementing with 30 mg carotene/day + 25,000 IU/ day retinyl palmitate on lung cancer risk. After finding almost 400 additional lung cancer incidents after four more years on an average, the experiment ended prematurely. Therefore, the researchers found that daily blend of β-carotene with retinyl palmitate could cause a negative effect on lung cancer incidence, and increase the likelihood of dying from cardiovascular complications, lung cancer, and other diseases caused in frequent smokers or asbestos workers. [100,106]. These studies' conclusions diverge from those of other research on supplemental β-carotene. Oral supplementation with doses up to 50 mg β-carotene on alternate days for up to 12 consecutive years seemed to have no negative effects on health in the Physicians' Health Study, which included 22,000 non-smoking male physicians. A supplement with a vitamin E and selenium additive comprising 15 mg of β-carotene

Table 3
Sources of the main carotenoids found in humans and daily intakes ranges.

Carotenoid	Daily intake ranges (mg)	Sources	References
α-Carotene	0.16 – 2.43	Carrots, palm oil	[100]
β-Carotene	0.92–8.80	Carrots, palm oil, gac oil, buriti, mango, sweet potato, apricot, green vegetables	[100]
β-Cryptoxanthin	0.04 – 1.36	Mandarins, tangerines, papaya, red pepper, persimmon, pitanga	[25,100]
Lutein + zeaxanthin	0.83 – 4.11	Sastra, green vegetables, egg yolk, pumpkin, sea buckthorn, marigold flower (lutein) Sastra, corozo, sapote, quince, orange pepper, red pepper, Chinese wolfberry, buriti, sea buckthorn, marigold flower (zeaxanthin)	[100,105]
Lycopene	0.83 – 9.43	Tomato, red papaya, red guava, watermelon, sarsaparilla, rose hip	[144]
Phytoene	2.00	Tomatoes, apricots, red peppers, carrots, red grapefruits, oranges	[145]
Phytofluene	0.70	Tomatoes, apricots, red peppers, carrots, red grapefruits, oranges	[145]

administered for 5 years was found to have an overall protective benefit for stomach cancer and total mortality in the Chinese Linxian intervention study, which comprised 30000 predominantly non-smokers and participants of both genders. When these four intervention trials are compared, some intriguing findings emerge. On the one hand, differences in the amount and form of β-carotene, co-administration with various compounds, unequal duration of interventions, and lifestyle factors affecting health (e.g., cigarette vapour or asbestos). Patients in the CARET studies and ATBC studies who were already at a higher risk of lung cancer were given large doses of -carotene (smokers and asbestos workers). In comparison to the other studies, these high dosages resulted in much greater plasma levels [99,106].

Animal (such as cancer-induced ferret or A/J mice subjects) as well as human research have now shown that certain factors, such as excessive drug intake, either pharmacological or dietary, as well as smoking can have a significant impact on the outcome of β-carotene supplementation at high dose. In animal subjects and non-smoking, apparently fit people, carotenoid supplement are frequently related with positive outcomes. Particularly, cell culture and in vivo studies examining the influences of β-carotene on lung carcinoma have shown in studies such as CARET and ATBC that, the negative effects of carotene in the lungs of smokers may contribute to the generation of oxidative metabolic products and other degradation materials from β-carotene [100,107]. In this consideration, there is mounting evidence that oxidative metabolites of carotenoids can have either good or harmful consequence relying on a variety of parameters, including their levels, which are mostly determined by the dosage and the amount of carotenoids or derivatives of carotenoids deposited within the tissue.

6. Conclusions and future visions

Dietary carotenoids and their mechanisms of action have been thoroughly investigated for therapeutic potential. Some carotenoids show promise in the treatment of respiratory disorders and may be the most effective alternative therapy. Although some clinical documentation for some carotenoids has been documented, a comprehensive evaluation of the toxicological aspects and interactions with other therapeutics is warranted. Detail studies on compositions, dose forms, pharmacokinetic parameter assessment, and safety are required. The identification and isolation of more potent carotenoids, as well as their mechanisms of action and compositions, should be the direction for future research. This research could pave the way for newly found drugs to enter clinical trials. Therefore, it has been determined that additional research into dietary carotenoids may result in the development of a novel class of therapeutic drug with immense potential and value.

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Fahadul Islam: Software, Data curation, Methodology, Formal analysis, Writing – original draft. **Maniza Muni:** Methodology, Validation, Visualization, Writing – original draft. **Saikat Mitra:** Conceptualization, Methodology, Investigation, Data Curation, Software, Formal analysis, Writing – original draft. **Talha Bin Emran:** Funding acquisition, Resources, Project administration, Writing – review & editing, Supervision. **Deepak Chandran:** Software, Data Curation, Writing – original draft. **Rajib Das:** Software, Data Curation, Writing – original draft. **Abdur Rauf:** Funding acquisition, Supervision, Resources, Writing – review & editing. **Sher Zaman Safi:** Project administration, Writing – review & editing. **Kumarappan Chidambaram:** Methodology, Validation, Visualization, Writing – original draft. **Manish Dhawan:** Methodology, Validation, Visualization, Writing – original draft. **Chunhoo Cheon:** Funding acquisition, Resources, Writing – review & editing. **Bonglee Kim:** Conceptualization, Funding acquisition, Supervision, Resources, Project administration, Writing – review & editing, Supervision.

Credit Author Statement

Authors have written their respective part in the paper therefore, all the authors have equally contributed to this paper under the supervision of Prof. Dr. Abdur Rauf.

Consent for publication

This does not involve any individual's data.

Ethics approval and consent to participate

The reported studies did not involve human participants and human data.

Conflict of interest statement

We declare no conflict of interest in submission of this manuscript.

Data Availability

Not applicable.

References

[1] S.P. Jadhav, H. Singh, S. Hussain, R. Gilhotra, A. Mishra, P. Prasher, A. Krishnan, G. Gupta, Introduction to lung diseases, Target. Cell. Signal. Pathw. Lung Dis. (2021) 1–25, https://doi.org/10.1007/978-981-33-6827-9_1.

[2] F. Schulze, X. Gao, D. Virzonis, S. Damiati, M.R. Schneider, R. Kodzius, Air quality effects on human health and approaches for its assessment through microfluidic chips, Genes (Basel) 8 (2017), https://doi.org/10.3390/genes8100244.

[3] J.B. Soriano, P.J. Kendrick, K.R. Paulson, V. Gupta, E.M. Abrams, R.A. Adedoyin, T.B. Adhikari, S.M. Advani, A. Agrawal, E. Ahmadian, F. Alahdab, S.M. Aljunid, K.A. Altirkawi, N. Alvis-Guzman, N.H. Anber, C.L. Andrei, M. Anjomshoa, F. Ansari, J.M. Antó, J. Arabloo, S.M. Athari, S.S. Athari, N. Awoke, A. Badawi, J. A.M. Banoub, D.A. Bennett, I.M. Bensenor, K.S.S. Berfield, R.S. Bernstein, K. Bhattacharyya, A. Bijani, M. Brauer, G. Bukhman, Z.A. Butt, L.A. Cámera, J. Car, J.J. Carrero, F. Carvalho, C.A. Castañeda-Orjuela, J.Y.J. Choi, D. J. Christopher, A.J. Cohen, L. Dandona, R. Dandona, A.K. Dang, A. Daryani, B. de Courten, F.M. Demeke, G.T. Demoz, J.W. De Neve, R. Desai, S.D. Dharmaratne, D. Diaz, A. Douiri, T.R. Driscoll, E.E. Duken, A. Eftekhari, H. Elkout, A.Y. Endries, I. Fadhil, A. Faro, F. Farzadfar, E. Fernandes, I. Filip, F. Fischer, M. Foroutan, M. A. Garcia-Gordillo, A.K. Gebre, K.B. Gebremedhin, G.G. Gebremeskel, K.E. Gezae, A.G. Ghoshal, P.S. Gill, R.F. Gillum, H. Goudarzi, Y. Guo, R. Gupta, G.B. Hailu, A. Hasanzadeh, H.Y. Hassen, S.I. Hay, C.L. Hoang, M.K. Hole, N. Horita, H. D. Hosgood, M. Hostiuc, M. Househ, O.S. Ilesanmi, M.D. Ilic, S.S.N. Irvani, S.M. S. Islam, M. Jakovljevic, A.A. Jamal, R.P. Jha, J.B. Jonas, Z. Kabir, A. Kasaeian, G. G. Kasahun, G.M. Kassa, A.T. Kefale, A.P. Kengne, Y.S. Khader, M.A. Khafaie, E. A. Khan, J. Khan, J. Khubchandani, Y.E. Kim, Y.J. Kim, S. Kisa, A. Kisa, L. D. Knibbs, H. Komaki, P.A. Koul, A. Koyanagi, G.A. Kumar, Q. Lan, S. Lasrado, P. Lauriola, C. La Vecchia, T.T. Le, J. Leigh, M. Levi, S. Li, A.D. Lopez, P.A. Lotufo, F. Madotto, N.B. Mahotra, M. Majdan, A. Majeed, R. Malekzadeh, A.A. Mamun, N. Manafi, F. Manafi, L.G. Mantovani, B.G. Meharie, H.G. Meles, G.G. Meles, R. G. Menezes, T. Mestrovic, T.R. Miller, G.K. Mini, E.M. Mirrakhimov, B. Moazen, K.A. Mohammad, S. Mohammed, F. Mohebi, A.H. Mokdad, M. Molokhia, L. Monasta, M. Moradi, G. Moradi, L. Morawska, S.M. Mousavi, K.I. Musa, G. Mustafa, M. Naderi, M. Naghavi, G. Naik, S. Nair, V. Nangia, J.R. Nansseu, J. Nazari, D.E. Ndwandwe, R.I. Negoi, T.H. Nguyen, C.T. Nguyen, H.L.T. Nguyen, M.R. Nixon, R. Ofori-Asenso, F.A. Ogbo, A.T. Olagunju, T.O. Olagunju, E. Oren, J.

R. Ortiz, M.O. Owolabi, M.P.A. DNB, S. Pakhale, A. Pana, S. Panda-Jonas, E. K. Park, H.Q. Pham, M.J. Postma, H. Pourjafar, H. Poustchi, A. Radfar, A. Rafiei, F. Rahim, M.H.U. Rahman, M.A. Rahman, S. Rawaf, D.L. Rawaf, L. Rawal, R. C. Reiner, M.B. Reitsma, L. Roever, L. Ronfani, E.M. Roro, G. Roshandel, K. E. Rudd, Y.D. Sabde, S. Sabour, B. Saddik, S. Safari, K. Saleem, A.M. Samy, M. M. Santric-Milicevic, B.P. Sao Jose, B. Sartorius, M. Satpathy, M. Savic, M. Sawhney, S.G. Sepanlou, M.A. Shaikh, A. Sheikh, M. Shigematsu, R. Shirkoohi, S. Si, S. Siabani, V. Singh, J.A. Singh, M. Soljak, R. Somayaji, M. Soofi, I.N. Soyiri, Y.M. Tefera, M.H. Temsah, B.E. Tesfay, J.S. Thakur, A.T. Toma, M. Tortajada-Girbés, K.B. Tran, B.X. Tran, L. Tudor Car, I. Ullah, M. Vacante, P.R. Valdez, J.F. M. van Boven, T.J. Vasankari, Y. Veisani, F.S. Violante, G.R. Wagner, R. Westerman, C.D.A. Wolfe, D.Z. Wondafrash, A.B. Wondmieneh, N. Yonemoto, S.J. Yoon, Z. Zaidi, M. Zamani, H.J. Zar, Y. Zhang, T. Vos, Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet Respir. Med. 8 (2020) 585–596, https://doi.org/10.1016/S2213-2600(20)30105-3.

[4] J.B. Soriano, A.A. Abajobir, K.H. Abate, S.F. Abera, A. Agrawal, M.B. Ahmed, A. N. Aichour, I. Aichour, M.T. Eddine Aichour, K. Alam, N. Alam, J.M. Alkaabi, F. Al-Maskari, N. Alvis-Guzman, A. Amberbir, Y.A. Amoako, M.G. Ansha, J. M. Antó, H. Asayesh, T.M. Atey, E.F.G.A. Avokpaho, A. Barac, S. Basu, N. Bedi, I. M. Bensenor, A. Berhane, A.S. Beyene, Z.A. Bhutta, S. Biryukov, D.J. Boneya, M. Brauer, D.O. Carpenter, D. Casey, D.J. Christopher, L. Dandona, R. Dandona, S.D. Dharmaratne, H.P. Do, F. Fischer, T.T. Gebrehiwot, A. Geleto, A.G. Ghoshal, R.F. Gillum, I.A. Mohamed Ginawi, V. Gupta, S.I. Hay, M.T. Hedayati, N. Horita, H.D. Hosgood, M.M.B. Jakovljevic, S.L. James, J.B. Jonas, A. Kasaeian, Y. S. Khader, I.A. Khalil, E.A. Khan, Y.H. Khang, J. Khubchandani, L.D. Knibbs, S. Kosen, P.A. Koul, G.A. Kumar, C.T. Leshargie, X. Liang, H. Magdy Abd El Razek, A. Majeed, D.C. Malta, T. Manhertz, N. Marquez, A. Mehari, G.A. Mensah, T.R. Miller, K.A. Mohammad, K.E. Mohammed, S. Mohammed, A.H. Mokdad, M. Naghavi, C.T. Nguyen, G. Nguyen, Q. Le Nguyen, T.H. Nguyen, D.N. A. Ningrum, V.M. Nong, J.I. Obi, Y.E. Odeyemi, F.A. Ogbo, E. Oren, P.A. Mahesh, E.K. Park, G.C. Patton, K. Paulson, M. Qorbani, R. Quansah, A. Rafay, M.H. U. Rahman, R.K. Rai, S. Rawaf, N. Reinig, S. Safiri, R. Sarmiento-Suarez, B. Sartorius, M. Savic, M. Sawhney, M. Shigematsu, M. Smith, F. Tadese, G. D. Thurston, R. Topor-Madry, B.X. Tran, K.N. Ukwaja, J.F.M. van Boven, V. V. Vlassov, S.E. Vollset, X. Wan, A. Werdecker, S.W. Hanson, Y. Yano, H. H. Yimam, N. Yonemoto, C. Yu, Z. Zaidi, M. El Sayed Zaki, A.D. Lopez, C.J. L. Murray, T. Vos, Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet Respir. Med. 5 (2017) 691–706, https://doi.org/10.1016/S2213-2600(17)30293-X.

[5] J.R. Maurer, Global and regional trends in COPD mortality, 1990-2010, 2016, Yearb. Pulm. Dis. (2016) 60–61, https://doi.org/10.1016/j.ypdi.2016.02.029.

[6] O. Enilari, S. Sinha, The global impact of asthma in adult populatio, Ann. Glob. Heal 85 (2019) 1–7, https://doi.org/10.5334/aogh.2412.

[7] I. Asher, N. Pearce, Global burden of asthma among children, Int. J. Tuberc. Lung Dis. 18 (2014) 1269–1278, https://doi.org/10.5588/ijtld.14.0170.

[8] C. Troeger, M. Forouzanfar, P.C. Rao, I. Khalil, A. Brown, S. Swartz, N. Fullman, J. Mosser, R.L. Thompson, R.C. Reiner, A. Abajobir, N. Alam, M.A. Alemayohu, A. T. Amare, C.A. Antonio, H. Asayesh, E. Avokpaho, A. Barac, M.A. Beshir, D. J. Boneya, M. Brauer, L. Dandona, R. Dandona, J.R.A. Fitchett, T.T. Gebrehiwot, G.B. Hailu, P.J. Hotez, A. Kasaeian, T. Khoja, N. Kissoon, L. Knibbs, G.A. Kumar, R.K. Rai, H.M.A. El Razek, M.S.K. Mohammed, K. Nielson, E. Oren, A. Osman, G. Patton, M. Qorbani, H.S. Roba, B. Sartorius, M. Savic, M. Shigematsu, B. Sykes, S. Swaminathan, R. Topor-Madry, K. Ukwaja, A. Werdecker, N. Yonemoto, M. El Sayed Zaki, S.S. Lim, M. Naghavi, T. Vos, S.I. Hay, C.J.L. Murray, A.H. Mokdad, Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015, Lancet Infect. Dis. 17 (2017) 1133–1161, https://doi.org/10.1016/S1473-3099(17)30396-1.

[9] R. Gasparini, D. Amicizia, P.L. Lai, D. Panatto, Clinical and socioeconomic impact of seasonal and pandemic influenza in adults and the elderly, Hum. Vaccin. Immunother. 8 (2012) 21–28, https://doi.org/10.4161/hv.8.1.17622.

[10] P. Dande, P. Samant, Acquaintance to Artificial Neural Networks and use of artificial intelligence as a diagnostic tool for tuberculosis: a review, Tuberculosis 108 (2018) 1–9, https://doi.org/10.1016/j.tube.2017.09.006.

[11] J. Didkowska, U. Wojciechowska, M. Mańczuk, J. Lobaszewski, Lung cancer epidemiology: contemporary and future challenges worldwide, Ann. Transl. Med. 4 (2016), https://doi.org/10.21037/atm.2016.03.11.

[12] J. Timoneda, L. Rodríguez-Fernández, R. Zaragozá, M.P. Marín, M.T. Cabezuelo, L. Torres, J.R. Viña, T. Barber, Vitamin A deficiency and the lung, Nutrients 10 (2018), https://doi.org/10.3390/nu10091132.

[13] T. Whyand, J.R. Hurst, M. Beckles, M.E. Caplin, Pollution and respiratory disease: Can diet or supplements help? A review, Respir. Res. 19 (2018), https://doi.org/10.1186/s12931-018-0785-0.

[14] H.J. Schünemann, S. McCann, B.J.B. Grant, M. Trevisan, P. Muti, J. L. Freudenheim, Lung function in relation to intake of carotenoids and other antioxidant vitamins in a population-based study, Am. J. Epidemiol. 155 (2002) 463–471, https://doi.org/10.1093/aje/155.5.463.

[15] D. Melo Van Lent, E.T.M. Leermakers, A. Hofman, B.H. Stricker, G.G. Brusselle, O. H. Franco, L. Lahousse, J.C.Kiefte-De Jong, Association between lutein intake and lung function in adults: the Rotterdam study, Br. J. Nutr. 117 (2017) 720–730, https://doi.org/10.1017/S0007114517000319.

[16] M.M. Heinen, B.A.J. Verhage, R.A. Goldbohm, P.A. Van Den Brandt, Intake of vegetables, fruits, carotenoids and vitamins C and e and pancreatic cancer risk in the Netherlands Cohort Study, Int. J. Cancer 130 (2012) 147–158, https://doi.org/10.1002/ijc.25989.

[17] W. Zhang, Y. Wang, W. Li, J. Du, Association between dietary carotenoid intakes and the risk of asthma in adults: a cross-sectional study of NHANES, 2007-2012, BMJ Open (2021) 2007–2012. https://lens.org/024-241-851-582-239.

[18] S. Mitra, A. Rauf, A.M. Tareq, S. Jahan, T. Bin Emran, T.G. Shahriar, K. Dhama, F. A. Alhumaydhi, A.S.M. Aljohani, M. Rebezov, M.S. Uddin, P. Jeandet, Z.A. Shah, M.A. Shariati, K.R. Rengasamy, Potential health benefits of carotenoid lutein: An updated review, Food Chem. Toxicol. 154 (2021), https://doi.org/10.1016/j.fct.2021.112328.

[19] G. Bjelakovic, D. Nikolova, C. Gluud, Meta-regression analyses, meta-analyses, and trial sequential analyses of the effects of supplementation with beta-carotene, vitamin A, and vitamin E singly or in different combinations on all-cause mortality: do we have evidence for lack of harm? PLoS One 8 (2013) https://doi.org/10.1371/journal.pone.0074558.

[20] L. Grievink, F.G. De Waart, E.G. Schouten, F.J. Kok, Serum carotenoids, α-tocopherol, and lung function among Dutch elderly, Am. J. Respir. Crit. Care Med. 161 (2000) 790–795, https://doi.org/10.1164/ajrccm.161.3.9904040.

[21] T.P. Ng, M. Niti, K.B. Yap, W.C. Tan, Dietary and supplemental antioxidant and anti-inflammatory nutrient intakes and pulmonary function, Public Health Nutr. 17 (2014) 2081–2086, https://doi.org/10.1017/S1368980013002590.

[22] I.F. Strati, V.J. Sinanoglou, L. Kora, S. Miniadis-Meimaroglou, V. Oreopoulou, Carotenoids from foods of plant, animal and marine origin: an efficient hplc-dad separation method, Foods 1 (2012) 52–65, https://doi.org/10.3390/foods1010052.

[23] T. Maoka, Carotenoids as natural functional pigments, J. Nat. Med. 74 (2020), https://doi.org/10.1007/s11418-019-01364-x.

[24] F. Delgado-Vargas, A.R. Jiménez, O. Paredes-López, F.J. Francis, Natural pigments: Carotenoids, anthocyanins, and betalains - characteristics, biosynthesis, processing, and stability, Crit. Rev. Food Sci. Nutr. 40 (2000) 173–289, https://doi.org/10.1080/10408690091189257.

[25] A.J. Meléndez-Martínez, A.I. Mandić, F. Bantis, V. Böhm, G.I.A. Borge, M. Brnčić, A. Bysted, M.P. Cano, M.G. Dias, A. Elgersma, M. Fikselová, J. García-Alonso, D. Giuffrida, V.S.S. Gonçalves, D. Hornero-Méndez, K. Kljak, V. Lavelli, G. A. Manganaris, P. Mapelli-Brahm, M. Marounek, B. Olmedilla-Alonso, M. J. Periago-Castón, A. Pintea, J.J. Sheehan, V. Tumbas Šaponjac, M. Valšíková-Frey, L. Van Meulebroek, N. O'Brien, A comprehensive review on carotenoids in foods and feeds: status quo, applications, patents, and research needs, Crit. Rev. Food Sci. Nutr. (2020), https://doi.org/10.1080/10408398.2020.1867959.

[26] N. Mezzomo, S.R.S. Ferreira, Carotenoids functionality, sources, and processing by supercritical technology: a review, J. Chem. (2016) (2016), https://doi.org/10.1155/2016/3164312.

[27] E. Toti, C.Y. Oliver Chen, M. Palmery, D.V. Valencia, I. Peluso, Non-provitamin A and provitamin A carotenoids as immunomodulators: recommended dietary allowance, therapeutic index, or personalized nutrition, Oxid. Med. Cell. Longev. (2018) (2018), https://doi.org/10.1155/2018/4637861.

[28] C.O. Perera, G.M. Yen, Functional properties of carotenoids in human health, Int. J. Food Prop. 10 (2007) 201–230, https://doi.org/10.1080/10942910601045271.

[29] H.E. Khoo, K.N. Prasad, K.W. Kong, Y. Jiang, A. Ismail, Carotenoids and their isomers: Color pigments in fruits and vegetables, Molecules 16 (2011) 1710–1738, https://doi.org/10.3390/molecules16021710.

[30] M.S. Taipina, L.C.A. Lamardo, N. Camilo Campos, M. Tavares, E. Gonzalez, L. I. Ferreira Jorge, S. Aued-Pimentel, Review of literature: carotenoids, chemical composition and dietary reference intake of buriti fruits, Int. J. Nutrology 06 (2013) 102–106, https://doi.org/10.1055/s-0040-1705679.

[31] M. Caseiro, A. Ascenso, A. Costa, J. Creagh-Flynn, M. Johnson, S. Simões, Lycopene in human health, Lwt 127 (2020), https://doi.org/10.1016/j.lwt.2020.109323.

[32] S. Przybylska, Lycopene – a bioactive carotenoid offering multiple health benefits: a review, Int. J. Food Sci. Technol. 55 (2020) 11–32, https://doi.org/10.1111/ijfs.14260.

[33] B. Eisenhauer, S. Natoli, G. Liew, V.M. Flood, Lutein and zeaxanthin — Food sources, bioavailability and dietary variety in age-related macular degeneration protection, Nutrients 9 (2017), https://doi.org/10.3390/nu9020120.

[34] A. Irías-Mata, V.M. Jiménez, C.B. Steingass, R.M. Schweiggert, R. Carle, P. Esquivel, Carotenoids and xanthophyll esters of yellow and red nance fruits (Byrsonima crassifolia (L.) Kunth) from Costa Rica, Food Res. Int. 111 (2018) 708–714, https://doi.org/10.1016/j.foodres.2018.05.063.

[35] R.K. Saini, S.H. Nile, S.W. Park, Carotenoids from fruits and vegetables: chemistry, analysis, occurrence, bioavailability and biological activities, Food Res. Int. 76 (2015) 735–750, https://doi.org/10.1016/j.foodres.2015.07.047.

[36] J.W. Mims, Asthma: Definitions and pathophysiology, Int. Forum Allergy Rhinol. 5 (2015) S2–S6, https://doi.org/10.1002/alr.21609.

[37] J. LJ, Airway smooth muscle as a target in asthma and the beneficial effects of bronchial thermoplasty, J. Allergy 2012 (2012), 593784. http://europepmc.org/articles/PMC3457660.

[38] Q. Hamid, M. Tulic, Immunobiology of asthma, Annu. Rev. Physiol. 71 (2009) 489–507, https://doi.org/10.1146/annurev.physiol.010908.163200.

[39] M. Kudo, Y. Ishigatsubo, I. Aoki, Pathology of asthma, Front. Microbiol. 4 (2013) 1–16, https://doi.org/10.3389/fmicb.2013.00263.

[40] U.M. Sahiner, E. Birben, S. Erzurum, C. Sackesen, O. Kalayci, Oxidative stress in asthma, World Allergy Organ. J. 4 (2011) 151–158, https://doi.org/10.1097/WOX.0b013e318232389e.

[41] S.C. Dharmage, J.L. Perret, A. Custovic, Epidemiology of asthma in children and adults, Front. Pediatr. 7 (2019) 246.

[42] S. Mitra, S.R. Prova, S.A. Sultana, R. Das, F. Nainu, T. Bin Emran, A.M. Tareq, M. S. Uddin, A.M. Alqahtani, K. Dhama, J. Simal-Gandara, Therapeutic potential of indole alkaloids in respiratory diseases: a comprehensive review, Phytomedicine 90 (2021), https://doi.org/10.1016/j.phymed.2021.153649.
[43] L.C. Hazlewood, L.G. Wood, P.M. Hansbro, P.S. Foster, Dietary lycopene supplementation suppresses Th2 responses and lung eosinophilia in a mouse model of allergic asthma, J. Nutr. Biochem 22 (2011) 95–100, https://doi.org/10.1016/j.jnutbio.2009.12.003.
[44] Y.H. Hwang, S.G. Hong, S.K. Mun, S.J. Kim, S.J. Lee, J.J. Kim, K.Y. Kang, S.T. Yee, The protective effects of astaxanthin on the OVA-induced asthma mice model, Molecules 22 (2017), https://doi.org/10.3390/molecules22112019.
[45] J.-Y. Song, C.-M. Lee, M.-K. Lee, Lutein modulates Th2 immune response in ovalbumin-induced airway inflammation, J. Life Sci. 22 (2012) 298–305, https://doi.org/10.5352/jls.2012.22.3.298.
[46] Y. Zhu, D. Sun, H. Liu, L. Sun, J. Jie, J. Luo, L. Peng, L. Song, Bixin protects mice against bronchial asthma though modulating PI3K/Akt pathway, Int. Immunopharmacol. 101 (2021), https://doi.org/10.1016/j.intimp.2021.108266.
[47] G.D. Rubenfeld, M.S. Herridge, Epidemiology and outcomes of acute lung injury, Chest 131 (2007) 554–562, https://doi.org/10.1378/chest.06-1976.
[48] P.R.M. Rocco, P. Pelosi, Pulmonary and extrapulmonary acute respiratory distress syndrome: Myth or reality? Curr. Opin. Crit. Care. 14 (2008) 50–55, https://doi.org/10.1097/MCC.0b013e3282f2405b.
[49] G.M. Matuschak, A.J. Lechner, Acute lung injury and the acute respiratory distress syndrome: pathophysiology and treatment, Mo. Med. 107 (2010) 252–258.
[50] K.J. Bosma, R. Taneja, J.F. Lewis, Pharmacotherapy for prevention and treatment of acute respiratory distress syndrome, Drugs 70 (2010) 1255–1282, https://doi.org/10.2165/10898570-000000000-00000.
[51] T. Muders, H. Wrigge, New insights into experimental evidence on atelectasis and causes of lung injury, Best. Pract. Res. Clin. Anaesthesiol. 24 (2010) 171–182, https://doi.org/10.1016/j.bpa.2010.02.009.
[52] J.D. Ricard, D. Dreyfuss, G. Saumon, Ventilator-induced lung injury, Eur. Respir, Journal Suppl. 22 (2003).
[53] M. Ragaller, T. Richter, Acute lung injury and acute respiratory distress syndrome, J. Emerg., Trauma Shock 3 (2010) 43–51, https://doi.org/10.4103/0974-2700.58663.
[54] R. Yang, L. Yang, X. Shen, W. Cheng, B. Zhao, K.H. Ali, Z. Qian, H. Ji, Suppression of NF-κB pathway by crocetin contributes to attenuation of lipopolysaccharide-induced acute lung injury in mice, Eur. J. Pharm. 674 (2012) 391–396, https://doi.org/10.1016/j.ejphar.2011.08.029.
[55] R. Li, P. Hong, X. Zheng, β-carotene attenuates lipopolysaccharide-induced inflammation via inhibition of the NF-κB, JAK2/STAT3 and JNK/p38 MAPK signaling pathways in macrophages, Anim. Sci. J. 90 (2019) 140–148, https://doi.org/10.1111/asj.13108.
[56] X. Wang, C. Zhang, C. Chen, Y. Guo, X. Meng, C. Kan, Allicin attenuates lipopolysaccharide-induced acute lung injuryin neonatal rats via the PI3K/Akt pathway, Mol. Med. Rep. 17 (2018) 6777–6783, https://doi.org/10.3892/mmr.2018.8693.
[57] S.W. Zito, Asthma and chronic obstructive pulmonary disease, Foye's Princ. Med. Chem. Seventh Ed. (2012) 1309–1345. https://doi.org/10.1016/b978–0-7020–7167-6.00012–9.
[58] A.D. Lopez, K. Shibuya, C. Rao, C.D. Mathers, A.L. Hansell, L.S. Held, V. Schmid, S. Buist, Chronic obstructive pulmonary disease: Current burden and future projections, Eur. Respir. J. 27 (2006) 397–412, https://doi.org/10.1183/09031936.06.00025805.
[59] S.A. Quaderi, J.R. Hurst, The unmet global burden of COPD, Glob. Heal. Epidemiol. Genom. 3 (2018), https://doi.org/10.1017/gheg.2018.1.
[60] W. Domej, K. Oettl, W. Renner, Oxidative stress and free radicals in COPD-implications and relevance for treatment, Int. J. COPD 9 (2014) 1207–1224, https://doi.org/10.2147/COPD.S51226.
[61] R. Lakhdar, S. Denden, A. Kassab, N. Leban, J. Knani, G. Lefranc, A. Miled, J. Ben Chibani, A.H. Khelil, Update in chronic obstructive pulmonary disease: Role of antioxidant and metabolizing gene polymorphisms, Exp. Lung Res. 37 (2011) 364–375, https://doi.org/10.3109/01902148.2011.580416.
[62] L. Taraseviciene-Stewart, N.F. Voelkel, Molecular pathogenesis of emphysema, J. Clin. Invest. 118 (2008) 394–402, https://doi.org/10.1172/JCI31811.
[63] A.R. Iskandar, C. Liu, D.E. Smith, K.Q. Hu, S.W. Choi, L.M. Ausman, X.D. Wang, β-cryptoxanthin restores nicotine-reduced lung SIRT1 to normal levels and inhibits nicotine-promoted lung tumorigenesis and emphysema in A/J mice, Cancer Prev. Res 6 (2013) 309–320, https://doi.org/10.1158/1940-6207.CAPR-12-0368.
[64] J.M. Rakic, C. Liu, S. Veeramachaneni, D. Wu, L. Paul, C.Y.O. Chen, L.M. Ausman, X.D. Wang, Lycopene inhibits smoke-induced chronic obstructive pulmonary disease and lung carcinogenesis by modulating reverse cholesterol transport in ferrets, Cancer Prev. Res 12 (2019) 421–432, https://doi.org/10.1158/1940-6207.CAPR-19-0063.
[65] Y. Xie, Q. He, H. Chen, Z. Lin, Y. Xu, C. Yang, Crocin ameliorates chronic obstructive pulmonary disease-induced depression via PI3K/Akt mediated suppression of inflammation, Eur. J. Pharm. 862 (2019), https://doi.org/10.1016/j.ejphar.2019.172640.
[66] K.K.D. Campos, G.R. Araújo, T.L. Martins, A.C.B. Bandeira, G. de, P. Costa, A. Talvani, C.C.M. Garcia, L.A.M. Oliveira, D.C. Costa, F.S. Bezerra, The antioxidant and anti-inflammatory properties of lycopene in mice lungs exposed to cigarette smoke, J. Nutr. Biochem 48 (2017) 9–20, https://doi.org/10.1016/j.jnutbio.2017.06.004.
[67] K.K.D. Campos, C. de Oliveira Ramos, T.L. Martins, G. de, P. Costa, A. Talvani, C. C.M. Garcia, L.A.M. Oliveira, S.D. Cangussú, D.C. Costa, F.S. Bezerra, Lycopene mitigates pulmonary emphysema induced by cigarette smoke in a murine model, J. Nutr. Biochem 65 (2019) 93–100, https://doi.org/10.1016/j.jnutbio.2018.12.008.
[68] S. Kasagi, K. Seyama, H. Mori, S. Souma, T. Sato, T. Akiyoshi, H. Suganuma, Y. Fukuchi, Tomato juice prevents senescence-accelerated mouse P1 strain from developing emphysema induced by chronic exposure to tobacco smoke, Am. J. Physiol. - Lung Cell. Mol. Physiol. 290 (2006), https://doi.org/10.1152/ajplung.00483.2004.
[69] C.S. Dela Cruz, L.T. Tanoue, R.A. Matthay, Lung cancer: epidemiology, etiology, and prevention, Clin. Chest Med. 32 (2011) 605–644, https://doi.org/10.1016/j.ccm.2011.09.001.
[70] W.D. Travis, E. Brambilla, G.J. Riely, New pathologic classification of lung cancer: Relevance for clinical practice and clinical trials, J. Clin. Oncol. 31 (2013) 992–1001, https://doi.org/10.1200/JCO.2012.46.9270.
[71] R. Nizzoli, M. Tiseo, F. Gelsomino, M. Bartolotti, M. Majori, L. Ferrari, M. De Filippo, G. Rindi, E.M. Silini, A. Guazzi, A. Ardizzoni, Accuracy of fine needle aspiration cytology in the pathological typing of non-small cell lung cancer, J. Thorac. Oncol. 6 (2011) 489–493, https://doi.org/10.1097/JTO.0b013e31820b86cb.
[72] M. Gómez-Morales, M. Cámara-Pulido, M.T. Miranda-León, A. Sánchez-Palencia, L. Boyero, J.A. Gómez-Capilla, M.E. Fárez-Vidal, Differential immunohistochemical localization of desmosomal plaque-related proteins in non-small-cell lung cancer, Histopathology 63 (2013) 103–113, https://doi.org/10.1111/his.12126.
[73] G.A. Silvestri, A.V. Gonzalez, M.A. Jantz, M.L. Margolis, M.K. Gould, L.T. Tanoue, L.J. Harris, F.C. Detterbeck, Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines, Chest. 143 (2013). https://doi.org/10.1378/chest.12–2355.
[74] S. Bernatsky, R. Ramsey-Goldman, M. Petri, M.B. Urowitz, D.D. Gladman, P. R. Fortin, E.H. Yelin, E. Ginzler, J.G. Hanly, C. Peschken, C. Gordon, O. Nived, C. Aranow, S.C. Bae, D. Isenberg, A. Rahman, J.E. Hansen, Y.S. Pierre, A. E. Clarke, Smoking is the most significant modifiable lung cancer risk factor in systemic lupus erythematosus, J. Rheuma 45 (2018) 393–396, https://doi.org/10.3899/jrheum.170652.
[75] E.D. Pleasance, P.J. Stephens, S. O'Meara, D.J. McBride, A. Meynert, D. Jones, M. L. Lin, D. Beare, K.W. Lau, C. Greenman, I. Varela, S. Nik-Zainal, H.R. Davies, G. R. Ordõez, L.J. Mudie, C. Latimer, S. Edkins, L. Stebbings, L. Chen, M. Jia, C. Leroy, J. Marshall, A. Menzies, A. Butler, J.W. Teague, J. Mangion, Y.A. Sun, S. F. McLaughlin, H.E. Peckham, E.F. Tsung, G.L. Costa, C.C. Lee, J.D. Minna, A. Gazdar, E. Birney, M.D. Rhodes, K.J. McKernan, M.R. Stratton, P.A. Futreal, P. J. Campbell, A small-cell lung cancer genome with complex signatures of tobacco exposure, Nature 463 (2010) 184–190, https://doi.org/10.1038/nature08629.
[76] L. Birt, N. Hall, J. Emery, J. Banks, K. Mills, M. Johnson, W. Hamilton, F. M. Walter, Responding to symptoms suggestive of lung cancer: A qualitative interview study, BMJ Open Respir. Res 1 (2014), https://doi.org/10.1136/bmjresp-2014-000067.
[77] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, Ca. Cancer J. Clin. 66 (2016) 7–30, https://doi.org/10.3322/caac.21332.
[78] A.C. Society, Cancer Facts & Figures 2016, Cancer Facts Fig. 2016. (2016) 1–9.
[79] T. Tanaka, M. Shnimizu, H. Moriwaki, Cancer chemoprevention by carotenoids, Molecules 17 (2012) 3202–3242, https://doi.org/10.3390/molecules17033202.
[80] Y.Z. Liu, C.M. Yang, J.Y. Chen, J.W. Liao, M.L. Hu, Alpha-carotene inhibits metastasis in Lewis lung carcinoma in vitro, and suppresses lung metastasis and tumor growth in combination with taxol in tumor xenografted C57BL/6 mice, J. Nutr. Biochem 26 (2015) 607–615, https://doi.org/10.1016/j.jnutbio.2014.12.012.
[81] W.L. Zhang, Y.N. Zhao, Z.Z. Shi, D. Cong, Y.S. Bai, Lutein inhibits cell growth and activates apoptosis via the PI3K/AKT/mTOR signaling pathway in A549 human non-small-cell lung cancer cells, J. Environ. Pathol. Toxicol. Oncol. 37 (2018) 341–350, https://doi.org/10.1615/JEnvironPatholToxicolOncol.2018027418.
[82] X. Jiang, H. Wu, W. Zhao, X. Ding, Q. You, F. Zhu, M. Qian, P. Yu, Lycopene improves the efficiency of anti-PD-1 therapy via activating IFN signaling of lung cancer cells, Cancer Cell Int 19 (2019), https://doi.org/10.1186/s12935-019-0789-y.
[83] J.C. Ko, J.C. Chen, T.J. Wang, H.Y. Zheng, W.C. Chen, P.Y. Chang, Y.W. Lin, Astaxanthin down-regulates Rad51 expression via inactivation of AKT kinase to enhance mitomycin C-induced cytotoxicity in human non-small cell lung cancer cells, Biochem. Pharmacol. 105 (2016) 91–100, https://doi.org/10.1016/j.bcp.2016.02.016.
[84] D. Chanda, E. Otoupalova, S.R. Smith, T. Volckaert, S.P. De Langhe, V. J. Thannickal, Developmental pathways in the pathogenesis of lung fibrosis, Mol. Asp. Med. 65 (2019) 56–69, https://doi.org/10.1016/j.mam.2018.08.004.
[85] P.L. Molyneaux, T.M. Maher, The role of infection in the pathogenesis of idiopathic pulmonary fibrosis, Eur. Respir. Rev. 22 (2013) 376–381, https://doi.org/10.1183/09059180.00000713.
[86] J.P. Finnerty, A. Ponnuswamy, P. Dutta, A. Abdelaziz, H. Kamil, Efficacy of antifibrotic drugs, nintedanib and pirfenidone, in treatment of progressive pulmonary fibrosis in both idiopathic pulmonary fibrosis (IPF) and non-IPF: a systematic review and meta-analysis, BMC Pulm. Med. 21 (2021), https://doi.org/10.1186/s12890-021-01783-1.
[87] S.R. Chilakapati, M. Serasanambati, P. Kumar, Manikonda, J.R. Kanala, Dietary lutein attenuates bleomycin-induced pulmonary fibrosis in mice, Int. J. Drug Deliv. 6 (2014) 380–388, https://doi.org/10.5138/ijdd.v6i4.1627.

[88] C. Zhou, W. Han, P. Zhang, M. Cai, D. Wei, C. Zhang, Lycopene from tomatoes partially alleviates the bleomycin-induced experimental pulmonary fibrosis in rats, Nutr. Res. 28 (2008) 122–130, https://doi.org/10.1016/j.nutres.2007.12.008.

[89] M.S. Zaghloul, E. Said, G.M. Suddek, H.A. Salem, Crocin attenuates lung inflammation and pulmonary vascular dysfunction in a rat model of bleomycin-induced pulmonary fibrosis, Life Sci. 235 (2019), https://doi.org/10.1016/j.lfs.2019.116794.

[90] H. Chen, J. Wang, R. Li, C. Lv, P. Xu, Y. Wang, X. Song, J. Zhang, Astaxanthin attenuates pulmonary fibrosis through lncITPF and mitochondria-mediated signal pathways, J. Cell. Mol. Med 24 (2020) 10245–10250, https://doi.org/10.1111/jcmm.15477.

[91] M. Wang, J. Zhang, X. Song, W. Liu, L. Zhang, X. Wang, C. Lv, Astaxanthin ameliorates lung fibrosis in vivo and in vitro by preventing transdifferentiation, inhibiting proliferation, and promoting apoptosis of activated cells, Food Chem. Toxicol. 56 (2013) 450–458, https://doi.org/10.1016/j.fct.2013.03.004.

[92] A. Sommer, K.S. Vyas, A global clinical view on vitamin A and carotenoids, Am. J. Clin. Nutr. 96 (2012), https://doi.org/10.3945/ajcn.112.034868.

[93] H.J. Schünemann, B.J.B. Grant, J.L. Freudenheim, P. Muti, R.W. Browne, J. A. Drake, R.A. Klocke, M. Trevisan, The relation of serum levels of antioxidant vitamins C and E, retinol and carotenoids with pulmonary function in the general population, Am. J. Respir. Crit. Care Med. 163 (2001) 1246–1255, https://doi.org/10.1164/ajrccm.163.5.2007135.

[94] S.O. Shaheen, K.A. Jameson, H.E. Syddall, A. Aihie Sayer, E.M. Dennison, C. Cooper, S.M. Robinson, The relationship of dietary patterns with adult lung function and COPD, Eur. Respir. J. 36 (2010) 277–284, https://doi.org/10.1183/09031936.00114709.

[95] R.D. Semba, S.S. Chang, K. Sun, S. Talegawkar, L. Ferrucci, L.P. Fried, Serum carotenoids and pulmonary function in older community-dwelling women, J. Nutr. Heal. Aging 16 (2012) 291–296, https://doi.org/10.1007/s12603-012-0034-z.

[96] V.P. Palace, N. Khaper, Q. Qin, P.K. Singal, Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease, Free Radic. Biol. Med. 26 (1999) 746–761, https://doi.org/10.1016/S0891-5849(98)00266-4.

[97] J. Fiedor, K. Burda, Potential role of carotenoids as antioxidants in human health and disease, Nutrients 6 (2014) 466–488, https://doi.org/10.3390/nu6020466.

[98] T.M. McKeever, S.A. Lewis, H.A. Smit, P. Burney, P.A. Cassano, J. Britton, A multivariate analysis of serum nutrient levels and lung function, Respir. Res. 9 (2008), https://doi.org/10.1186/1465-9921-9-67.

[99] M. Eggersdorfer, A. Wyss, Carotenoids in human nutrition and health, Arch. Biochem. Biophys. 652 (2018) 18–26, https://doi.org/10.1016/j.abb.2018.06.001.

[100] A.J. Meléndez-Martínez, An overview of carotenoids, apocarotenoids, and vitamin a in agro-food, nutrition, health, and disease, Mol. Nutr. Food Res. 63 (2019) 1–11, https://doi.org/10.1002/mnfr.201801045.

[101] T. Mehmood, A. Ahmed, Z. Ahmed, Food-grade nanoemulsions for the effective delivery of β-carotene, Langmuir (2021), https://doi.org/10.1021/acs.langmuir.0c03399.

[102] R. Ravikrishnan, S. Rusia, G. Ilamurugan, U. Salunkhe, J. Deshpande, J. Shankaranarayanan, M.L. Shankaranarayana, M.G. Soni, Safety assessment of lutein and zeaxanthin (Lutemax™ 2020): Subchronic toxicity and mutagenicity studies, Food Chem. Toxicol. 49 (2011) 2841–2848, https://doi.org/10.1016/j.fct.2011.08.011.

[103] J.A. Edwards, Zeaxanthin: review of toxicological data and acceptable daily intake, J. Ophthalmol. (2016) (2016), https://doi.org/10.1155/2016/3690140.

[104] J. Berman, U. Zorrilla-López, G. Farré, C. Zhu, G. Sandmann, R.M. Twyman, T. Capell, P. Christou, Nutritionally important carotenoids as consumer products, Phytochem. Rev. 14 (2015) 727–743, https://doi.org/10.1007/s11101-014-9373-1.

[105] M. Rodriguez-Concepcion, J. Avalos, M.L. Bonet, A. Boronat, L. Gomez-Gomez, D. Hornero-Mendez, M.C. Limon, A.J. Meléndez-Martínez, B. Olmedilla-Alonso, A. Palou, J. Ribot, M.J. Rodrigo, L. Zacarias, C. Zhu, A global perspective on carotenoids: Metabolism, biotechnology, and benefits for nutrition and health, Prog. Lipid Res. 70 (2018) 62–93, https://doi.org/10.1016/j.plipres.2018.04.004.

[106] K.J. Meyers, et al., Genetic evidence for role of carotenoids in age-related macular degeneration in the carotenoids in age-related eye disease study (CAREDS), Investig. Ophthalmol. Vis. Sci. 55 (2014) 587–599, http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L372233090%0Ahttp://www.iovs.org/content/55/1/587.full.pdf%0Ahttps://doi.org/10.1167/iovs.13-13216.

[107] C. Wang, S. Zhao, X. Shao, J. Bin Park, S.H. Jeong, H.J. Park, W.J. Kwak, G. Wei, S.W. Kim, Challenges and tackles in metabolic engineering for microbial production of carotenoids, Microb. Cell Fact. 18 (2019), https://doi.org/10.1186/s12934-019-1105-1.

[108] J. Wang, J. Kuai, Z. Luo, W. Wang, L. Wang, C. Ke, X. Li, Y. Ni, Crocin attenuates lipopolysacchride-induced acute lung injury in mice, Int. J. Clin. Exp. Pathol. 8 (2015) 4844–4850.

[109] A.A. El-Kholy, M.A. Elkablawy, D.S. El-Agamy, Lutein mitigates cyclophosphamide induced lung and liver injury via NF-κB/MAPK dependent mechanism, Biomed. Pharmacother. 92 (2017) 519–527, https://doi.org/10.1016/j.biopha.2017.05.103.

[110] X. Li, R. Huang, K. Liu, M. Li, H. Luo, L. Cui, L. Huang, L. Luo, Fucoxanthin attenuates LPS-induced acute lung injury via inhibition of the TLR4/MyD88 signaling axis, Aging (Albany NY) 13 (2021) 2655–2667, https://doi.org/10.18632/aging.202309.

[111] W.W. Li, T.Y. Wang, B. Cao, B. Liu, Y.M. Rong, J.J. Wang, F. Wei, L.Q. Wei, H. Chen, Y.X. Liu, Synergistic protection of matrine and lycopene against lipopolysaccharide-induced acute lung injury in mice, Mol. Med. Rep. 20 (2019) 455–462, https://doi.org/10.3892/mmr.2019.10278.

[112] S. Türkoğlu, M.H. Muz, R. Özercan, F. Gürsu, G. Kirkil, Effects of lycopene on the model of oleic acid-induced acute lung injury, Tuberk. Toraks 60 (2012) 101–107, https://doi.org/10.5578/tt.2468.

[113] X. Cai, Y. Chen, X. Xie, D. Yao, C. Ding, M. Chen, Astaxanthin prevents against lipopolysaccharide-induced acute lung injury and sepsis via inhibiting activation of MAPK/NF-κB, Am. J. Transl. Res. 11 (2019) 1884–1894.

[114] J. Bi, R. Cui, Z. Li, C. Liu, J. Zhang, Astaxanthin alleviated acute lung injury by inhibiting oxidative/nitrative stress and the inflammatory response in mice, Biomed. Pharmacother. 95 (2017) 974–982, https://doi.org/10.1016/j.biopha.2017.09.012.

[115] X. Li, R. Huang, H. Luo, Explor. Mech. astaxanthin lipopolysaccharide-Induc. acute lung Inj. Netw. Pharmacol. Exp. Valid. (2021) 1–20.

[116] W. Xu, M. Wang, G. Cui, L. Li, D. Jiao, B. Yao, K. Xu, Y. Chen, M. Long, S. Yang, J. He, Astaxanthin protects OTA-induced lung injury in mice through the Nrf2/NF-κB pathway, Toxins (Basel) 11 (2019), https://doi.org/10.3390/toxins11090540.

[117] J. Ding, J. Su, L. Zhang, J. Ma, Crocetin activates Foxp3 through TIPE2 in asthma-associated treg cells, Cell. Physiol. Biochem. 37 (2015) 2425–2433, https://doi.org/10.1159/000438595.

[118] J. Wu, Y. Zhang, Q. Liu, W. Zhong, Z. Xia, All-trans retinoic acid attenuates airway inflammation by inhibiting Th2 and Th17 response in experimental allergic asthma, BMC Immunol. 14 (2013), https://doi.org/10.1186/1471-2172-14-28.

[119] H. Polat, M. Sagıt, S.G. Gurgen, M. Yasar, I. Ozcan, Protective role of lycopene in experımental allergic rhinitis in rats, Int. J. Pediatr. Otorhinolaryngol. 150 (2021), https://doi.org/10.1016/j.ijporl.2021.110905.

[120] Z. Zainal, A.A. Rahim, H. Khaza'ai, S.K. Chang, Effects of palm oil tocotrienol-rich fraction (TRF) and carotenes in ovalbumin (OVA)-challenged asthmatic brown Norway rats, Int. J. Mol. Sci. 20 (2019), https://doi.org/10.3390/ijms20071764.

[121] S.J. Wu, C.J. Liou, Y.L. Chen, S.C. Cheng, W.C. Huang, Fucoxanthin ameliorates oxidative stress and airway inflammation in tracheal epithelial cells and asthmatic mice, Cells 10 (2021), https://doi.org/10.3390/cells10061311.

[122] D.D. Haines, B. Varga, I. Bak, B. Juhasz, F.F. Mahmoud, H. Kalantari, R. Gesztelyi, I. Lekli, A. Czompa, A. Tosaki, Summative interaction between astaxanthin, Ginkgo biloba extract (EGb761) and vitamin C in Suppression of respiratory inflammation: a comparison with ibuprofen, Phyther. Res. 25 (2011) 128–136, https://doi.org/10.1002/ptr.3160.

[123] H. Kubo, K. Asai, K. Kojima, A. Sugitani, Y. Kyomoto, A. Okamoto, K. Yamada, N. Ijiri, T. Watanabe, K. Hirata, T. Kawaguchi, Astaxanthin suppresses cigarette smoke-induced emphysema through Nrf2 activation in mice, Mar. Drugs 17 (2019), https://doi.org/10.3390/md17120673.

[124] N. Liu, W. Zhang, S. Luo, J. Cao, M. Peng, Z. Liu, Astaxanthin suppresses cigarette smoke and lipopolysaccharide-induced airway inflammation through induction of heme oxygenase-1, Cell. Mol. Biol. 65 (2019) 94–99, https://doi.org/10.14715/cmb/2019.65.1.17.

[125] J. Levy, E. Bosin, B. Feldman, Y. Giat, A. Miinster, M. Danilenko, Y. Sharoni, Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene, Nutr. Cancer 25 (1995) 257–266.

[126] F. Lian, D.E. Smith, H. Ernst, R.M. Russell, X.D. Wang, Apo-10′-lycopenoic acid inhibits lung cancer cell growth in vitro, and suppresses lung tumorigenesis in the A/J mouse model in vivo, Carcinogenesis 28 (2007) 1567–1574, https://doi.org/10.1093/carcin/bgm076.

[127] K.S. Liao, C.L. Wei, J.C. Chen, H.Y. Zheng, W.C. Chen, C.H. Wu, T.J. Wang, Y. S. Peng, P.Y. Chang, Y.W. Lin, Astaxanthin enhances pemetrexed-induced cytotoxicity by downregulation of thymidylate synthase expression in human lung cancer cells, Regul. Toxicol. Pharmacol. 81 (2016) 353–361, https://doi.org/10.1016/j.yrtph.2016.09.031.

[128] M. Mehrabani, M. Goudarzi, S. Mehrzadi, A. Siahpoosh, M. Mohammadi, H. Khalili, A. Malayeri, Crocin: a protective natural antioxidant against pulmonary fibrosis induced by bleomycin, Pharmacol. Rep. 72 (2020) 992–1001, https://doi.org/10.1007/s43440-019-00023-y.

[129] G. Kirkil, M.H. Muz, E. Sanvaktar, D. Kaman, K. Sahin, O. Kucuk, The effect of lycopene supplementation on chronic obstructive lung disease, Nobel Med 8 (2013) 98–104.

[130] C. Hanson, E. Lyden, L. Weissenburger-Moser, J. Furtado, D.J. Romberger, T. D. Levan, Serum level of nutritional antioxidants are decreased in veteran smokers with, COPD, J. Mil. Veterans Health 25 (2017) 26–34.

[131] M. Rautalahti, J. Virtamo, J. Haukka, O.P. Heinonen, J. Sundvall, D. Albanes, J. K. Huttunen, The effect of alpha-tocopherol and beta-carotene supplementation on COPD symptoms, Am. J. Respir. Crit. Care Med. 156 (1997) 1447–1452, https://doi.org/10.1164/ajrccm.156.5.96-11048.

[132] S. Rerksuppaphol, L. Rerksuppaphol, Carotenoid intake and asthma prevalence in Thai children, Pediatr. Rep. 4 (2012), https://doi.org/10.4081/pr.2012.e12.

[133] L.G. Wood, P.G. Gibson, M.L. Garg, R.J. Blake, S. Garcia-Caraballo, Airway and circulating levels of carotenoids in asthma and healthy controls, J. Am. Coll. Nutr. 24 (2005) 448–455, https://doi.org/10.1080/07315724.2005.10719490.

[134] L.G. Wood, M.L. Garg, J.M. Smart, H.A. Scott, D. Barker, P.G. Gibson, Manipulating antioxidant intake in asthma: A randomized controlled trial1-3, Am. J. Clin. Nutr. 96 (2012) 534–543, https://doi.org/10.3945/ajcn.111.032623.

[135] L.G. Wood, M.L. Garg, H. Powell, P.G. Gibson, Lycopene-rich treatments modify noneosinophilic airway inflammation in asthma: Proof of concept, Free Radic. Res. 42 (2008) 94–102, https://doi.org/10.1080/10715760701767307.

[136] I. Neuman, H. Nahum, A. Ben-Amotz, Reduction of exercise-induced asthma oxidative stress by lycopene, a natural antioxidant, Allergy Eur. J. Allergy Clin. Immunol. 55 (2000) 1184–1189, https://doi.org/10.1034/j.1398-9995.2000.00748.x.

[137] O. Aibana, M.F. Franke, C.C. Huang, J.T. Galea, R. Calderon, Z. Zhang, M. C. Becerra, E.R. Smith, A.G. Ronnenberg, C. Contreras, R. Yataco, L. Lecca, M. B. Murray, Impact of Vitamin A and carotenoids on the risk of tuberculosis progression, Clin. Infect. Dis. 65 (2017) 900–909, https://doi.org/10.1093/cid/cix476.

[138] T.A.-T. and B.C.C.P.S. Group, The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers, N. Engl. J. Med. 330 (1990) 1029–1035.

[139] M.M. Society, Lack of Effect of Long-Term Supplementation With Beta Carotene on the Incidence of Malignant Neoplasms and Cardiovascular Disease, N. Engl. J. Med. 334 (2007) 1145–1149.

[140] W.J. Blot, J.-Y. Li, P.R. Taylor, B. Li, Lung cancer and vitamin supplementation, 614–614, N. Engl. J. Med. 331 (1994), https://doi.org/10.1056/nejm199409013310913.

[141] V. Spate, J.S. Morris, Serum micronutrients and the subsequent risk of oral and pharyngeal cancer, Cancer Res 53 (1993) 795–798.

[142] G.S. Omenn, G.E. Goodman, M.D. Thornquist, J. Balmes, M.R. Cullen, A. Glass, J. P. Keogh, F.L. Meyskens, B. Valanis, J.H. Williams, S. Barnhart, S. Hammar, Effects of a Combination of Beta Carotene and Vitamin a on Lung Cancer and Cardiovascular Disease, N. Engl. J. Med 334 (1996) 1150–1155.

[143] S. Asbaghi, A. Saedisomeolia, M. Hosseini, N. Mohammadzadeh Honarvar, A. Khosravi, E. Azargashb, Dietary Intake and Serum Level of carotenoids in lung cancer patients: a case-control study, Nutr. Cancer 67 (2015) 893–898, https://doi.org/10.1080/01635581.2015.1055365.

[144] E. Murillo, D. Giuffrida, D. Menchaca, P. Dugo, G. Torre, A.J. Meléndez-Martinez, L. Mondello, Native carotenoids composition of some tropical fruits, Food Chem. 140 (2013) 825–836, https://doi.org/10.1016/j.foodchem.2012.11.014.

[145] E. Biehler, F. Mayer, L. Hoffmann, E. Krause, T. Bohn, Comparison of 3 spectrophotometric methods for carotenoid determination in frequently consumed fruits and vegetables, J. Food Sci. 75 (2010), https://doi.org/10.1111/j.1750-3841.2009.01417.x.