



Utilization of antioxidants and anti-inflammatory compounds in managing SARS-CoV-2 infection to achieve healthy community: A review



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ABSTRACT

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The COVID-19 outbreak has struck the world and has led to mortalities worldwide. On top of that, cancer diseases are the other major cause of death globally. Scientists around the globe are racing to find possible therapeutic compounds that could alleviate or manage these diseases. Searching for the potential compounds to be utilised as a treatment for SARS-CoV-2 infection and immunotherapies for cancer is in line with achieving a healthy community. The healthy community concept aims to reduce health gaps regardless of the status quo within a community. In making this concept a success, the ability to recover from health disasters such as cancer and the COVID-19 outbreak is one of the indicators. It could be achieved when humans are supplemented with proper nutrients to help manage these diseases. Studies have suggested that compounds exhibiting anti-inflammatory and antioxidant properties could help to reduce the inflammation caused by the SARS-CoV-2 infection while enhancing the immune system to address cancer diseases. The current work will review the anti-inflammatory properties of astaxanthin, tocotrienols and tocopherols, plus the beta-carotene and fucoxanthin's antioxidant properties. The potential of the studied compounds to be utilised as cancer immunotherapies will be further evaluated, as these compounds have also been reported to exhibit anti-cancer properties. The findings of this study will indicate the potential of these five compounds in managing SARS-CoV-2 infection and act as cancer immunotherapies in achieving a healthy community.

Contribution/ Originality: Though the anti-inflammatory and antioxidant of the compounds were widely reported, the information on the relationship between the ability of the compound and its impact in achieving a healthy community, especially in managing SARS-CoV-2 infection and cancer diseases, was minimal. Hence, the current work aims to narrow the research gaps.

1. INTRODUCTION

A healthy community is a growing concept that aims to narrow the health gaps among the citizens in a community. This concept is in line with the WHO concept regarding community health. In short, a healthy community is a branch of health that focuses on people and their role in caring for their well-being. Achieving a healthy community could include getting proper nutrients and supplementations and quickly recovering from health disasters [1, 2]. The COVID-19 pandemic has affected and killed countless human lives globally. The first reported pneumonia case caused by a novel coronavirus was identified in December 2019 in Wuhan, Hubei, China. Due to its fast transmission by aerosols and air, World Health Organization (WHO) declared the disease a Global pandemic in January 2020 [3].

The causative agent of COVID-19 is the 2019 novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a Coronaviridae family species. SARS-CoV-2 has a more robust and faster ability of transmission to cause infection across the globe than the past coronavirus cases, making it hard to control instantly [4]. Few articles suggested that COVID-19 patients should receive nutritional support to complete their diet. Even people who are not infected by COVID-19 need to consider this. It is suggested that these infected individuals consume supplements that may have anti-inflammatory and antioxidant properties [5]. Instead of the COVID-19 outbreak, cancer is the other leading cause of death worldwide. In 2020, approximately 10 million deaths occurred due to cancer. It is one of the problems that greatly influenced human life and became the main challenge for doctors and patients. In making a healthy community a reality, more potential compounds to be utilised in developing cancer immunotherapies should be further discovered [6].

Antioxidants and anti-inflammatory compounds could be the potential candidates to manage COVID-19 and act as potential immunotherapies for cancer diseases in achieving Healthy Community. In biological terms, any substance that may slow or stop the action of oxidants is considered an antioxidant. Furthermore, antioxidants work together to neutralise reactive oxygen species (ROS) and reactive nitrogen species (RNS), reducing oxidative cell and tissue damage [7]. Conversely, anti-inflammation refers to pro-inflammatory mediators' lowering or removing action responsible for acute and chronic inflammation. These actions can be accomplished by limiting their synthesis, stopping their activity by selective antagonists or extracellular scavenger molecules, or breaking down or modifying the enzymatic post-translational [8].

Many compounds exhibit anti-inflammatory and antioxidant properties. Nevertheless, astaxanthin, tocotrienols and tocopherol will be reviewed for their anti-inflammatory properties, while fucoxanthin and beta-carotene's antioxidant properties will be further evaluated. This current work will review their potential to manage the recent COVID-19 outbreak and cancer diseases by providing proper supplementations to humankind in achieving a healthy community.

2. REVIEWED ANTIOXIDANT AND ANTI-INFLAMMATORY COMPOUNDS

Antioxidants can suppress or considerably retard the oxidation of easily oxidisable compounds like lipids to prevent cell damage. These compounds can oxidise themselves before or rather than other molecules [9]. Various anti-inflammatory compounds have been extensively studied and transformed into therapeutic agents to enhance pharmacology, decrease side effects and recognise new targets. Anti-inflammatory compounds vary from endogenous or natural to synthetic and neutralising antibody-based molecules. The short-term or moderate use of anti-inflammatory regimes is safe and effective against inflammation. However, long-term use of anti-inflammatory compounds, particularly in treating chronic inflammation, will lead to notable side effects in specific organs and increase the risk of immunosuppression [10, 11]. The current work will review the anti-inflammatory properties of astaxanthin, tocopherol and tocotrienols plus antioxidants such as beta carotene and fucoxanthin in managing COVID-19 and utilisation of these compounds as immunotherapies for cancer diseases in achieving a healthy community.

2.1. Astaxanthin

Astaxanthin (3,30dihydroxy-, -carotene-4,40-dione) is a keto-carotenoid that exerts a broad range of health-promoting qualities via its interactions with a diverse array of molecular targets [12]. Yeast, bacteria, and some algae, most notably derived from *Haematococcus pluvialis*, are sources of astaxanthin. It can also be discovered in some fish, crustaceans, and birds because of how food chains work in nature, which makes astaxanthin accumulate [13]. *H. pluvialis* is the primary source of human consumption of astaxanthin. When exposed to high salinity, nitrogen depletion, hot temperatures, and light, the freshwater microalga *H. pluvialis* can acquire significant astaxanthin (up to 3.8–5% of the microalga's dry mass) [12, 14]. Astaxanthin generally protects against oxidative damage, including neutralised singlet oxygen, scavenging radicals to avoid chain reactions, preserving membrane structure by retarding lipid peroxidation (LPO) and enhancing the immune system function and gene expression modulation [12]. Astaxanthin is widely used in industries and comes from chemical (artificial) and natural sources. Synthetic astaxanthin has a 20-fold lower antioxidant capacity than natural astaxanthin and is 95% available in the market. Dietary astaxanthin is the only Food and Drug Administration (FDA)-approved astaxanthin [14].

2.2. Tocopherol

Tocotrienols and tocopherols are lipid-soluble tocols compounds in four different structures: alpha, beta, gamma, and delta, as shown in Figure 1 [15]. These four isoforms have different locations and numbers of methyl groups [16].

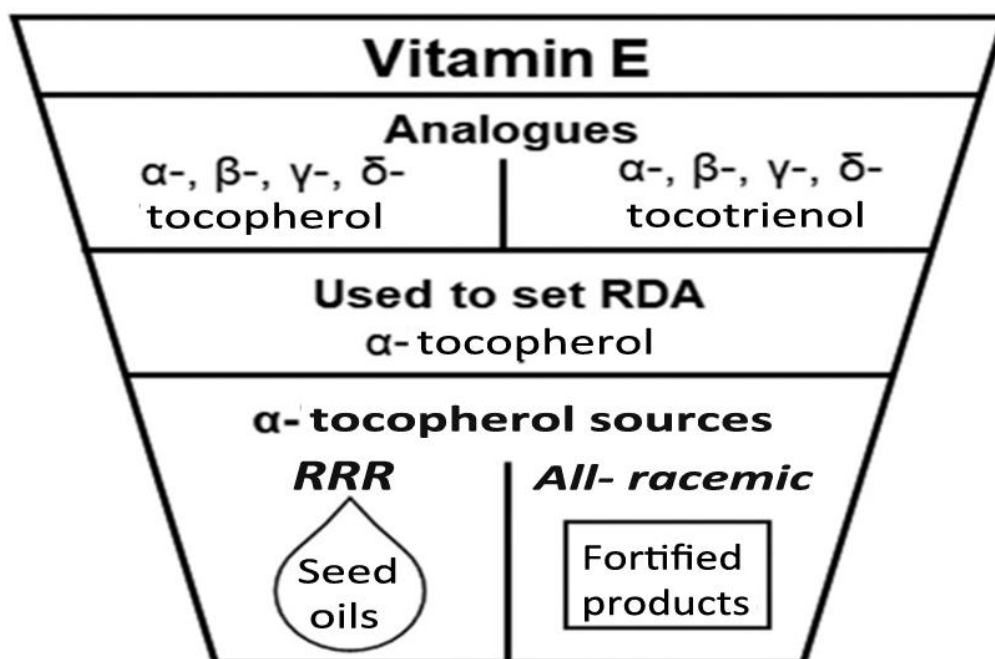


Figure 1. Form of vitamin E.

Note: α -, β -, γ -, δ - refer to alpha-, beta-, gamma-, and delta-tocopherols and the alpha-, beta-, gamma-, and delta-tocotrienols, the analogues of vitamin E. Alpha-tocopherol has been used to set the Recommended Dietary Allowance for vitamin E. RRR refers to natural sources of alpha-tocopherols (usually derived from seed oils), while *All-racemic* refers to synthetic sources of alpha-tocopherol (usually derived from fortified products).

They are differentiated by the number and location of the methyl group bonded to the chroman nucleus. Tocopherols have a saturated lateral chain; meanwhile, tocotrienols have it in an unsaturated form and an isoprenoid side chain [17]. Studies have revealed that, out of these four isomers, α -Tocopherol (α -T) is considered a primary form of vitamin E (VE) in animals. It exhibits the highest activity in performing essential antioxidant functions VE. The anti-cancer properties of α -Tocopherol have been extensively studied due to the action of oxidative stress in carcinogenesis [18]. Generally, there are two sources of α -tocopherol, naturally occurring α -

tocopherol isomers known as RRR α -tocopherol and the synthetic all-racemic α -tocopherol. Both of this α -tocopherol are generally consumed via dietary supplements and foods. Studies suggested that naturally occurring α -tocopherol has a notable effect on human health compared with synthetic ones. Due to the mentioned facts, scientists and researchers around the globe are studying plants that exhibit effective vitamin E content [17-19]. Seed oils are some examples of naturally occurring α -tocopherol, while ready-to-eat cereals could be regarded as a source of synthetic α -tocopherol. A study suggested that adults take 15 mg of naturally occurring alpha-tocopherol (RRR α -tocopherol) daily. The anti-inflammatory potential of tocopherol has been studied for several areas of human health, including the immune system, cancer, the central nervous system, and the cardiovascular system [15, 18, 19].

2.3. Tocotrienols

Vitamin E can be found naturally in vegetables, plants and plant oils, and tocotrienols are generally found in the monocotyledonous plants' seeds, dicotyledonous plants' fruits and latex of rubber trees. Tocotrienols are mainly extracted from rice bran, palm, and annatto seeds. These three sources were considered primary sources of tocotrienols [20]. Other sources of tocotrienols include coconut oil, barley germ, wheat germ, maize, grapefruit seed oil, hazelnuts, rye, flaxseed oil, olive oil, Buckthorn berry and sunflower oil [21]. The tocopherol ratio to tocotrienol is 4.5:5.5 in rice bran oil, 30:70 in palm oil and 0:100 in annatto seeds, as shown in Figure 2 [22].

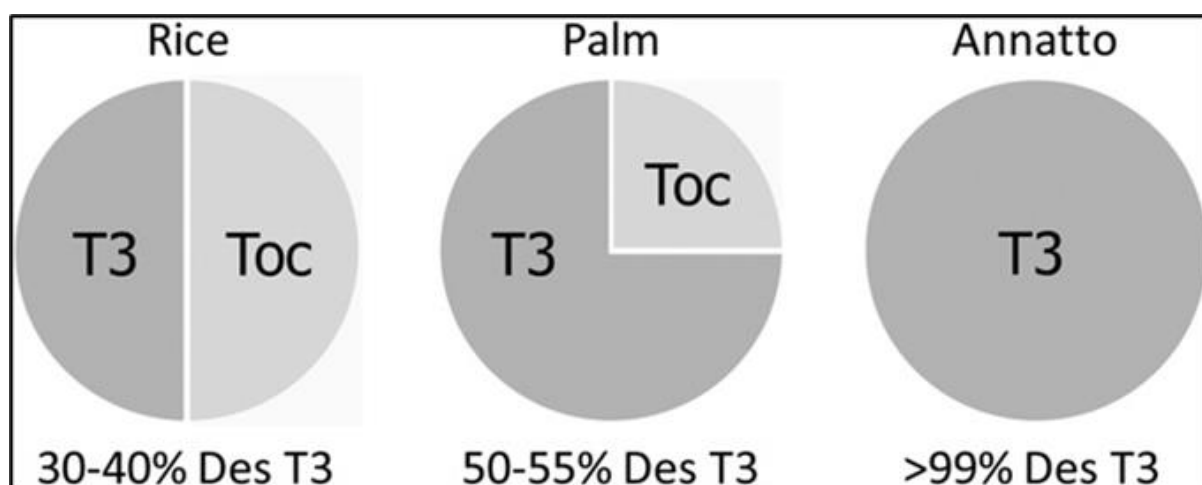


Figure 2. The distribution of tocotrienol(T3) in three primary sources.

Note: In rice, 30-40% of Tocotrienols (T3) were comprised of delta-tocotrienols (Des T3), 50-55% and more than 99% of Tocotrienols found in Palm and Annatto consisted of delta-tocotrienols (Des T3), respectively.

In oil palm, approximately 75% of the vitamin E comes from tocotrienols, with a majority of γ -tocotrienols [20]. Many studies have revealed that palm oil carries anti-oxidative properties with potential therapeutics in the pharmaceutical industry. The antioxidants in palm oil involve a bouquet of compounds, including tocotrienols and carotenes. Tocotrienol is reported to own superior anti-inflammatory, antioxidant, anti-cancer, and neuroprotective properties, while it helps reduce cholesterol levels in plasma [21-23]. The current work will further evaluate the anti-inflammatory properties of tocotrienols. In the current work, the anti-inflammatory properties of tocotrienols will be further evaluated.

2.4. Fucoxanthin

Fucoxanthin is a xanthophyll carotenoid prevalent in macroalgae, and it is found primarily on kelp (brown algae seaweeds) and microalgae (diatoms) and is critical for algal photosynthesis [24]. Diatoms, such as *Phaeodactylum tricorutum*, are recommended sources of fucoxanthin in the food industry due to their higher fucoxanthin concentration extraction efficiency and shorter growing cycle than macroalgae [25, 26]. On top of

that, fucoxanthin can scavenge singlet molecular oxygen and peroxy radicals. Energy transfer between two molecules is the primary mechanism for carotenoids to quench singlet oxygen. For carotenoids to quench singlet oxygen, energy transfer between two molecules is the primary mechanism. An inert ground state of carotenoid molecules and a triplet excited state of carotenoid molecules are formed by the transference of energy from oxidation to the conjugated double bonds in carotenoids. To get the carotenoids back to their normal state, they release energy into the atmosphere. Consequently, it is possible to reuse carotenoids because they are not oxidised or consumed by the process. Carotenoids are more effective in quenching singlet oxygen when they have more conjugated double bonds. Additionally, carotenoids scavenge for free radicals. In the terminal rings of carotenoids, functional elements, such as carbonyl and hydroxyl groups, influence their ability to scavenge free radicals [24-26]. Several chronic medical conditions, including heart disease, type 2 diabetes and obesity, hypertension, and osteoporosis, have been shown to benefit from fucoxanthin's antioxidant and scavenger properties for ROS, inflammation-related disorders, and its antibacterial carotenoid properties [26]. Besides, this beneficial pigment has demonstrated promising potential in preventing skin photoaging in UVB-irradiated hairless mice [27]. Additionally, because fucoxanthin is safe for animals, it can be utilised in various feed items [28].

2.5. Beta-Carotene

Beta-carotene is the most significant pro-vitamin A carotenoid, and they are usually found in algae, plants, and photosynthetic microorganisms that range from yellow to red. *Dunaliella salina* is a halotolerant green microalga with the highest source of β -carotene among microalgae. *D. salina* is frequently cultured in salinity conditions and is used in various industries, including pharmaceutical, health, food, and energy [29, 30]. Apart from that, Beta-carotene is insoluble in water, moderately soluble in ethanol and ether, and somewhat soluble in chloroform, benzene, and oil. It has a melting point of 176–180 °C [30]. The disease-preventive effect of β -carotene and other pro-vitamin A carotenoids can be attributed to their conversion to retinoids or their activity as whole molecules [31]. Beta-carotene has been found to have anti-cancer and antioxidant characteristics, assisting in protecting human and animal skin from photoaging, which also helps manage cholesterol levels to reduce the risk of cardiovascular disease [14, 30, 31]. Different fields can benefit from the use of carotenoids. As a food colourant, beta-carotene has been widely employed in the food industry, including in the production of soft beverages, pastries, and margarine. The European Commission has authorised beta-carotene from *Dunaliella salina* as a food colourant (E160 an (iv) Algal Carotenes) [29]. Besides, there are numerous health benefits associated with carotenoids, such as lowering triglyceride levels while boosting HDL (high-density lipoprotein) cholesterol and avoiding cancer, which is why they are utilised in nutraceuticals [14, 32]. Most beta-carotene in the industry is synthetic and contains just the all-trans isomer. Beta-carotene is a useful pigment found in various microalgal species. Still, microalgae's poor beta-carotene production has become a critical barrier to industrialisation [29].

3. COVID-19

The COVID-19 pandemic, caused by SARS-CoV-2, has significantly impacted healthcare systems as it may cause pneumonia, with symptoms that vary from mild to severe [33]. Researchers have struggled to develop a treatment option for managing the infection. It is noted that antioxidants and anti-inflammatory are essential nutrients that humans cannot synthesise naturally, and inadequate amounts must be taken from diet or supplementation [34]. SARS-CoV-2 infection may also lead to oxidative stress, which later may cause pulmonary dysfunction, cytokine storm, and viral sepsis, while worsening COVID-19 impact in certain people [35]. This is because oxidative stress appears to have a role in developing viral pathogens and other lung illnesses, making antioxidant therapy a viable treatment option for the lower respiratory tract [36].

Numerous research indicates several novel ways of boosting the immune system. These include immunisation, conventional therapy, and supplementation with antioxidants and vitamins. Treatments primarily focus on

symptomatic and respiratory support, with many nations adopting WHO recommendations. In clinical trials, many cures, such as antioxidants and vitamins, are still being searched for, but their efficacy is still uncertain [37]. COVID-19 has no approved treatments; nonetheless, preventative measures such as taking health supplements, social isolation, public sanitation, and wearing face masks are the most effective current treatments. Furthermore, as it has been proved that certain micronutrients are crucial to the immune system, individuals are beginning to take antioxidants and vitamins to boost their immune systems. There are concerns that the SARS-CoV-2 spike protein constantly changes, resulting in the discovery of potential variants [36-38].

Individuals infected with SARS-CoV-2 may experience severe flu-like symptoms, eventually leading to renal failure, pneumonia, acute respiratory distress (ARD) and death. A study has reported that out of 99 studied patients, 83% experience fever, 82% and 31% experience cough and dyspnea, respectively [38, 39]. Another study revealed that patients who experienced ARD and multiorgan failures due to SARS-CoV-2 infection require mechanical ventilation to support respiration [40]. A study reported that infected individuals would require urgent treatment before a severe inflammatory response occurs, known as the cytokine storm phase [41, 42]. Tissue damage in the immune or epithelial cells due to SARS-CoV-2 infection has led to the release of inflammatory cytokines such as IL-1, IL-12, IL-6 and TNF- α . Consequently, these cytokines will call up innate immune cells such as macrophages and monocytes, thus activating the adaptive immune cells, CD4+ T cells and CD8+ T cells. Activating these adaptive immune cells led to myelopoiesis and granulopoiesis [40, 41, 43].

Several treatments have been discovered for treating the inflammation caused by SARS-CoV-2 infection. Among these treatments, methylprednisolone and dexamethasone, known as Corticosteroids, were regarded as options to treat infected individuals with cytokine storm as a low dose prescription of these agents reduces the mortality of critically ill patients that requires mechanical ventilation. Nevertheless, using these agents might have long-term complications and delayed viral clearance. Intravenous Immunoglobulin (II) is another option to treat inflammation caused by SARS-CoV-2 infection. II has been proven to exert an immunomodulatory effect primarily by neutralising the virus via antibodies/polyclonal immunoglobulin G (IgG) [42, 44, 45]. Chloroquine and Hydroxychloroquine are other drugs being prescribed to manage COVID-19-infected individuals. These compounds could lessen the glycosylation of ACE-2 receptors, thus averting SARS-CoV-2 from binding to host cells effectively [44, 45].

Based on the facts mentioned earlier, there is a need to find the potential natural compounds that exhibit anti-inflammatory properties as therapeutic agents to alleviate the inflammation caused by the SARS-CoV-2 infection.

3.1. Cancer Diseases

Cancer is a disease that occurs due to mutation in genes. An oncogene is a gene that undergoes a mutation, leading to cancer development. In their normal condition, oncogenes are known as proto-oncogenes that regulate cell division. When proto-oncogenes turn mutated, they can become overactive and cause cells to divide uncontrollably. It causes abnormality in the regulation of cellular pathways that results in higher multiplication and survival of cancer cells [46]. They can avoid the damaging effects of the immune response of the immune system to survive and proliferate. Cancer cells may spread and develop from the area they first formed to the surrounding tissues. It is called metastatic cancer, which involves the metastasis process.

Metastasis is the dissemination of tumour cells from the primary tumour site to the other sites through multiple steps, commonly in the advanced cancer stage [47]. The treatment could be further divided into two; traditional and modern treatment in treating cancer diseases. Surgery is one of the traditional modalities that is widely used. It is preferred over chemotherapy and radiotherapy as it causes minimum harm to the surrounding tissues. It yields excellent effectiveness at the early stage of cancer. It can be done through open or minimally invasive surgery. Open surgery makes a huge slit and commonly causes the tumour and some healthy tissues to be removed. Oppositely, minimally invasive surgery makes small slits instead of huge ones and involves a laparoscope

for viewing the tumour [48, 49].

Meanwhile, radiation relates to using ionising radiation to destroy cancer cells. It can cause cancer cells to be killed directly or genetically modify them to undergo apoptosis and thus die. The destructed DNA have lost the ability to increase and leads the cell division process to be suppressed. As a result, they die. On the other hand, chemotherapy inhibits tumour development by eliminating their ability to divide and initiate cell death. Chemotherapy causes changes in tumour cells to stop their growth development or cause them to die. Different types of drugs can be used in chemotherapy. For instance, alkylating agents, anti-metabolites, anthracyclines and more [50].

Angiogenesis inhibitor is one of the advanced modalities to treat cancer. It involves using chemical inhibitors to inhibit the blood from being supplied to the tumour cells by blocking the blood vessels growth. Examples of inhibitors include thalidomide, interferon, bevacizumab and more [49, 51]. Another modern cancer treatment will be emphasised and focused on in this study. It is known as immunotherapies. Immunotherapies stimulate the immune system to recognise and eliminate cancer cells in a host body [52]. Thus, the potential compounds to be utilised as cancer immunotherapies should be further evaluated.

3.2. Anti-inflammatory Properties of the Studied Compound

Inflammation is an immune system's protective defence response when unwanted foreign materials or pathogens infect the tissue cells or when the local tissue is injured [50]. These immune responses comprise a complicated cascade of pro and anti-inflammatory mediators [51]. Immune homeostasis is a state of immunological equilibrium achieved by maintaining the balance of effector immune cells and regulatory immune cells. These cells act by removing the disease or pathogens by carrying out an immunostimulatory role or hindering the excess inflammation by performing a regulatory role [52]. Inflammation can be derived into two; acute and chronic inflammation. Acute inflammation is a typical response of our body's immune system to heal wounds and fight infections; meanwhile, chronic inflammation may be a symptom of inflammatory diseases [53]. Two types of cytokines are involved in the regulatory roles of inflammation: pro-inflammatory cytokines and anti-inflammatory cytokines. The pro-inflammatory cytokines act by promoting inflammation to eradicate the invasion of pathogens. Anti-inflammatory cytokines, on the other hand, control the pro-inflammatory cytokine response. At the beginning of inflammation, macrophages release growth factors and recruit fibroblasts to produce collagen in the tissue. The stimuli are eliminated in the initial phase of inflammation. After removing stimuli, the synthesis of pro-inflammatory mediators is blocked, the existing inflammatory mediators in the tissue are digested. Finally, the recruitments of white blood cells and polymorphonuclear neutrophils (PMNs) are inhibited. The lipoxins and cyclopentenone prostaglandins (cyPGs) play significant roles in anti-inflammatory activities. The lipoxins block the gene expression of adhesion molecules, stop the migration of neutrophils, inhibit superoxide production, and assist the apoptosis of neutrophils. The cyPGs demonstrate anti-inflammatory effects by suppressing the expression of adhesion molecules on endothelium and inducible nitric oxide synthase by macrophages [53, 54]. When the inflammation is uncontrollable, or the acute inflammatory response fails to discard the stimulation, acute inflammation may evolve into chronic inflammation. Chronic inflammation is linked to the development of numerous inflammatory diseases such as cancer, cardiovascular and pulmonary diseases, Alzheimer's disease, diabetes and obesity, and rheumatoid arthritis [50]. Chronic inflammation occurs when there are ongoing tissue injuries and attempts at tissue healing, consistent infections that may turn into delayed hypersensitive disorders and the presence of toxic agents. In autoimmune diseases or hypersensitive disorders, the immune system overreacts to itself, leading to chronic inflammation. In the severe cases of COVID-19, immune dysregulation shows a progressive pattern. Pro-inflammatory cytokines and chemokines are higher in patients with severe illnesses and ventilated patients [54, 55].

3.3. Astaxanthin and Anti-Inflammatory Properties

Astaxanthin has been reported to reduce inflammation, apoptosis, and oxidative stress by controlling different oxidative stress pathways, as oxidative stress has been reported to play a role in disease onset, progression, and critical complications. When astaxanthin is administered orally or parenterally to animal models, it is reported that this carotenoid improves insulin secretion and resistance while reducing hyperglycemia. The carotenoid also deploys protective repercussions over neuropathy, nephropathy, and retinopathy [56]. In an inflammatory state, macrophages were reported to bind with low-density lipoproteins (LDL) through scavenger receptors like SR-A, SR-B2 (CD36) and LOX-1. As a result, many pro-inflammatory mediators, including cytokines, NO, chemokines, cyclooxygenase-2 (COX-2), plus matrix metalloproteinases (MPPs), were produced. It is reported that supplementation with 10 μ M of astaxanthin reduced SR-A and CD36 receptor expression. Consequently, pro-inflammatory markers like interleukin (IL)-1 β , IL-6, tumour necrosis factor- α (TNF- α), inducible nitric oxide synthase (iNOS), and COX-2 have been reported to reduce in concentration when astaxanthin was applied or ingested [57]. On the other hand, dry eye disease (DED) will usually lead to hyperosmolarity, causing pro-inflammatory stress to the ocular surface epithelium. It is reported that astaxanthin has successfully lessened the expression of High-mobility group box 1 (HMGB1) and hindered the increment of TNF- α and IL-1 β while promoting phospho-Akt (p-Akt) expression. The study suggested that astaxanthin could relieve the DED [58].

3.4. Tocotrienol and Anti-Inflammatory Properties

The role of tocotrienols as anti-inflammation *in vitro* includes inhibiting the proliferation of breast cancer cells. Besides, one recent study reveals that γ -tocotrienol is effective as a potent anti-osteoporosis agent due to its anti-inflammatory properties. This is done by the action of γ -tocotrienol that elevates genes associated with osteoblastogenesis and regulates A20, an inhibitor of NF- κ B, to prevent osteoclastogenesis in murine RAW264.7 bone-marrow-derived macrophages. A combinational therapy with resveratrol, quercetin, and δ -tocotrienol demonstrates the inhibition of Nitric Oxide (NO) production and C-reactive protein (CRP) levels, a marker of systemic inflammation, resulting in improved efficacy in the prevention of age-related illnesses. Other than that, tocotrienols extracted from muscadine grape seed oil inhibit adipose inflammation in human adipocytes by lowering mRNA and protein expression of peroxisome proliferator-activated receptor (PPAR) γ and adaptor protein (AP)-2 [59]. A mouse peritoneal macrophage study indicated that tocotrienols protected against NO and pro-inflammatory cytokines better than α -tocopherol and α -tocopheryl [60]. Apart from that, the role of tocotrienols as anti-inflammatory *in vivo* includes the ability of tocotrienols to directly bind to antioxidant enzymes, enhancing their protective effect in silicon docking. In another study to prove the anti-inflammatory properties of tocotrienols, scientists administered 10mg of naturally occurring tocotrienol daily for 10 days in a group of Syrian hamsters before challenging them with compounds to induce massive free radicals plus oxidative stress that resembles acute localised and systemic inflammation. The scientists also revealed that when tocotrienols (10 mg/kg) were given orally for 10 days, plasma and lipoprotein lipids, cholesterol, Apo-B, small dense low-density lipoprotein (LDL), and LDL in hyperlipidemia-induced hamsters were all reduced [59, 60]. In rats, treatment with δ -tocotrienol and γ -tocotrienol resulted in a considerable reduction in organ inflammation compared to treatment with α -tocopherol. In that work, obese Zucker rats and control lean Zucker rats aged 8 weeks were fed an enriched diet for 20 weeks, with either 1% or 5% water-soluble rice bran enzymatic extract high in polyphenols, tocotrienols, or γ -oryzanol, resulting in decreased obesity-related pro-inflammatory responses [61]. In hepatocellular cancer, tocotrienols combined with biodegradable epirubicin nanoparticles significantly reduced oxidative stress, inflammation, apoptosis, and angiogenesis (HCC) [62].

3.5. Tocopherol and Anti-Inflammatory Properties

Tocopherol supplementation has also been associated with reducing serum levels of pro-inflammatory

mediators, suggesting a specific role in inflammation related to renal and urologic affections. Most of the data regarding the action of tocopherol in Diabetic Kidney Disease (DKD) are available from pre-clinical studies, mainly confirming the effects of supplementation on reducing pro-inflammatory mediators and oxidation markers and improving clinical parameters of renal function and kidney histology [63, 64]. In fact, according to some observations, α -tocopherol seems to exert a more significant inhibitory activity on Protein Kinase-C (PKC) than β -tocopherol, probably interacting with a peculiar enzyme isoform. This may be due to additional mechanisms portrayed by α -tocopherol, such as inhibiting the lipoxygenase pathway [64]. A study has applied alpha-tocopherol (α -TOH) in murine cardiac ischemia/reperfusion injury induced by ligation of the left anterior descending coronary artery for 60 min. α -TOH significantly reduced infarct size, restored cardiac function as measured by ejection fraction, fractional shortening, cardiac output, and stroke volume, and prevented pathological changes as assessed by state-of-the-art strain and strain-rate analysis. The expression of inflammatory and oxidative markers is down-regulated by α -TOH, indicating its anti-inflammatory properties [65]. In another study, two treatments options, fish oil (FO) intravenous lipid emulsions (ILEs) and fish oil added with α -tocopherol, were used as a monotherapy to treat parenteral nutrition (PN)-associated liver disease and provide essential fatty acids (EFAs) needed to sustain growth and prevent EFA deficiency (EFAD). Adding α -tocopherol to FO improved the inflammatory response to endotoxin challenge compared with FO-ILE alone, suggesting that α -tocopherol is a potent anti-inflammatory compound [64-66]. Compared to tocotrienols, anti-inflammatory properties of tocopherol are not widely being discovered. Based on the facts mentioned earlier, the anti-inflammatory properties of astaxanthin, tocotrienols, and tocopherols should be considered when finding potential therapeutic agents in addressing the recent SARS-CoV-2 outbreak. The ability of these anti-inflammatory compounds to reduce inflammation by downregulating the pro-inflammatory markers should be considered significant in managing the inflammation caused by the SARS-CoV-2 infection.

3.6. Antioxidant Properties of the Studied Compound

Antioxidants are chemical molecules that attach to free oxygen radicals and protect healthy cells from damage. Endogenous antioxidants are generated in the body, while exogenous antioxidants are obtained from nutrition (exogenous) [7]. They interact with free radicals and stop a chain reaction before damaging essential components. In biological terms, any substance that may slow or stop the action of oxidants is considered an antioxidant. Furthermore, antioxidants work together to neutralise reactive oxygen species (ROS) and reactive nitrogen species (RNS), reducing oxidative cell and tissue damage. Antioxidants are usually defined by their ability to donate hydrogen or electrons [67]. Antioxidants are classified as enzymatic or non-enzymatic. Enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) are produced endogenously in humans and defence against free radicals under normal circumstances. Antioxidants naturally occurring in an organism may help combat oxidative stress caused by various physiological processes [9]. However, enzymatic antioxidants are impaired in neutralising free radicals under severe illness conditions [68]. Hence, external dietary antioxidants are needed to bolster the human defence mechanism. Antioxidants that are non-enzymatic or have a low molecular weight affect the function of cellular redox equilibrium. Non-enzymatic antioxidants in nature include polyphenols, carotenoids, and vitamins found in fruits and vegetables [69]. Antioxidants have demonstrated beneficial qualities for humans. Antioxidants suppress the formation of free radicals both in vivo and in vitro. They also extend the shelf life of food and medications by minimising the damage caused by oxidative stress [9, 67, 68]. As an outcome, antioxidants are widely used in various industries, including the pharmaceutical, cosmetic, and food industries. Infectious diseases were no longer the dominant concern in industrialised countries throughout the last decade in the pharmaceutical industry. Instead, non-infectious diseases, such as cardiovascular disease and cancer, contributed to most illness and death cases. Excess free radicals in the body is a primary cause of relevant chronic disease [67-69].

3.7. Fucoxanthin and its Antioxidant Properties

Fucoxanthin is one of many carotenoids with antioxidant properties that can scavenge singlet molecular oxygen and peroxy radicals [24-26]. Studies have shown that fucoxanthin can support a variety of critical biological activities and can also be used to treat various health issues. Several chronic medical conditions, including heart disease, type 2 diabetes and obesity, hypertension and osteoporosis, have been shown to benefit from fucoxanthin's antioxidant and scavenger properties for ROS, inflammation-related disorders, and its antibacterial carotenoid properties [26]. Fucoxanthin can effectively prevent oxidative damage in HepG2 cells induced by arachidonic acid (AA) and iron and reduce oxides and inflammation in the liver. Excessive AA induces extremely high cellular and mitochondrial ROS levels, adversely affecting promoting mitochondrial permeability transition. Pretreatment with fucoxanthin blocked the ability of AA and iron to induce harmful effects in HepG2. It induced a significant increase in the phosphorylation of ULK1 and AMPK and expression of the autophagy marker beclin-1 [70].

3.8. Beta carotene and its Antioxidant Properties

Previous studies have indicated that adherence to a diet with high antioxidant properties, especially with β -Carotene, may reduce the risk of all-cause mortality [71, 72]. In one study, soy protein isolate (SPI)-Pleurotus eryngii polysaccharide (PEP) conjugate was prepared by Maillard reaction under controlled wet-heating conditions. β -Carotene was encapsulated in SPI-PEP conjugate-stabilized emulsion, and its gastrointestinal behaviour and antioxidant activity were assessed in vitro. Such improvement favoured β -carotene to relieve tert-butyl hydroperoxide-induced oxidative stress by decreasing reactive oxygen species production and enhancing antioxidant enzyme activities in Caco-2 cells. The study suggested that Maillard-type protein-polysaccharide conjugates-stabilised emulsions had a potential industry application for delivering fat-soluble nutrients [73]. Moreover, it has been suggested that there is a close relationship between the deficiency of vitamins and infectious diseases such as tuberculosis, AIDS, and CoV-2 SARS, and infectious diseases spread through the respiratory and digestive systems [74]. Antioxidant properties of β -Carotene were not widely reported, and further studies related to this compound must be further evaluated.

It could be noted that the antioxidant properties of fucoxanthin and beta-carotene have allowed scientists and researchers around the globe to study more about these compounds. With previous experiments that have been done before, the antioxidant properties of these compounds shall be evaluated further in terms of their ability to be utilised as cancer immunotherapies.

3.9. Healthy Community

A healthy community is one in which local groups from all parts of the community work together to prevent disease and make healthy living options accessible. Working at the community level to promote healthy living brings tremendous health benefits to the most significant number of people. It also helps reduce health gaps caused by differences in income, education, race and ethnicity, location, and other health factors [1]. A healthy community is one in which multiple sectors collaborate to improve the conditions that influence human health and well-being. Well-being refers to the presence of the highest possible quality of life, including good living standards, robust health, a sustainable environment, vital communities, an educated populace, balanced time use, high levels of democratic participation, and access to and participation in leisure and culture [1, 2, 75]. SARS-CoV-2 and cancer diseases are two leading death causes worldwide. Finding ways to manage these diseases could lead to a healthy community, as one of the success criteria is resolving health disasters quickly [2].

3.10. Fucoxanthin and Beta-Carotene in Achieving a Healthy Community

Consuming proper nutrition and supplementation rich in antioxidant and anti-inflammatory properties could

help the community achieve a healthy community [76]. VA (retinol) is essential for the general health of humans. The essential pro-vitamin A carotenoid is β -carotene, present in carrots and yellow and green leafy vegetables. Carotenoids, including α - and β -carotene and α -tocopherol, are detected in the human dermis and epidermis. The presence of carotenoids in the skin protects against damage caused by the photooxidative processes. Carotenoids and other antioxidants can eliminate reactive oxygen species and absorb UV light through dietary supplements and topical applications [76, 77]. Table 1 indicates the various application of beta-carotene supplementation.

Table 1. Various applications of beta-carotene supplementation.

Strains	Subject used	Results	References
<i>D. salina</i>	Male and female <i>Drosophila melanogaster</i>	<i>D. salina</i> extracts usage has enhanced the median lifespans of the subject used due to the improvement of mitochondrial by the 9-cis- β - carotene.	Wang, et al. [77]
	Adult male albino Wistar rats	<i>D. salina</i> extracts have preserved the rats studied against TAA-induced hepatic fibrosis.	
	Wistar rats	Carotenoid extracts from <i>D. salina</i> have exhibited better antioxidant activity than synthetic carotene in rat liver homogenates.	
<i>S. platensis</i>	Cows	The supplementation of 5% spray-dried <i>S. platensis</i> containing β -carotene has enhanced the milk contents in the cows compared to the control group.	
<i>B. braunii</i>	Male Wistar rats	The study suggested that β - carotene extracts from the strains show antioxidant activity by reducing the free and hydroxyl-radicals while preventing lipid peroxidation.	
<i>S. platensis</i> , <i>B. braunii</i> and <i>H. pluvialis</i>	Male Wistar rats	Rats supplemented by the supplementation have higher antioxidant enzymes in the blood and liver when compared with the controls.	

In animal studies, no toxicity of fucoxanthin was observed. Food and Drug Administration allowed fucoxanthin extracted from the alga, *Phaeodactylum tricornutum*, as a new dietary ingredient consumed at 3 mg daily with no time limit or 5 mg fucoxanthin for up to 90 days [26]. Figure 3 illustrates the health benefits of fucoxanthin in achieving a healthy community.

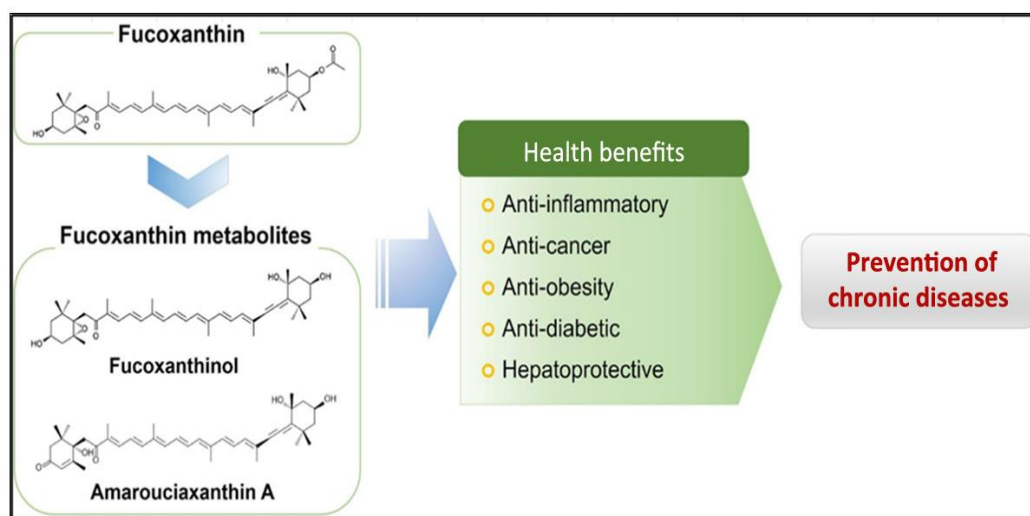


Figure 1. Health benefits of fucoxanthin.

3.11. Astaxanthin, Tocopherol and Tocotrienols in Achieving a Healthy Community

Astaxanthin (AX) has been consumed for approximately twenty years as a nutritional supplement. The primary source has been a natural plant-based supplement from the single-cell alga *Haematococcus pluvialis* (NAT-AX). Recently, astaxanthin from other sources has entered the marketplace. The primary alternative source in the human nutritional supplement market has been a synthetic form of astaxanthin produced from petrochemicals (SYN-AX). Additionally, a minimal amount of astaxanthin from a genetically-manipulated yeast *Xanthophyllomyces dendrorhous* (former nomenclature *Phaffia rhodozyma*, still commonly referred to as "*Phaffia*") (PH-AX) is also available in some supplement products. NAT-AX demonstrated 14X to 90X more significant antioxidant activity than SYN-AX in head-to-head antioxidant experiments. In numerous animal trials in diverse species, NAT-AX in esterified form has demonstrated superior efficacy in increasing lifespan; treating skin cancer; preventing the formation of gastric ulcers; improving stress resistance; decreasing reactive oxygen species (ROS); increasing retinol conversion in the liver; augmenting enzyme levels; increasing growth rates; and improving exercise endurance [12, 13, 78]. Many studies have also been carried out in groups of patients with different diseases, such as in diabetics at a dose of 3mg/kg under treatment for sixty days [25], patients with hyperlipidemia, and aortic stenosis at doses of 240mg/day for two years [26], with no reports of adverse effects. Patients with more severe conditions, such as diabetic nephropathy [27], evaluated tocotrienols' activity in type 2 diabetic patients with renal impairment. This study treated patients with two daily doses of 200mg of tocotrienols for eight weeks. According to the authors, 400mg is the maximum approved by the Food and Drug Administration (FDA). There were no reports of side effects or changes in plasma biochemistry parameters among the results acquired. The anti-inflammatory activity of T3 has also been proposed to protect against neurodegenerative diseases, including Alzheimer's disease (AD) and alcohol-induced cognitive impairment in rats. Suppression of inflammation is also among the mechanisms by which T3 can neutralise the ability of cancer cells to proliferate, metastasise, escape apoptotic signals, and develop chemoresistance. Finally, low intake and serum levels of tocopherols and tocotrienols have been associated with age-related pathologies, including osteoporosis, sarcopenia, and cognitive impairment [78-80]. Intestinal failure-associated liver disease (IFALD) is a risk of parenteral nutrition (PN)-dependence. This study suggests a hepatoprotective role for α -tocopherol in liver injury induced by the enteral administration of a parenteral nutrition solution. Phytosterols do not appear to compromise the hepatoprotective effects of fish oil [46].

3.12. Cancer Immunotherapies

Cancer immunotherapy is a type of cancer treatment related to the modulation of the immune system to eradicate cancer cells. Thus, it provides better protection to the host body from the cancer cells' activity with the help of immune agents like vaccines, cytokines and others [81]. It stimulates the host's anti-cancer reaction by elevating the number of effector cells and forming soluble mediators that allow tumour-killing conditions [82]. The effectors recognise and kill the malignant cells while guarding the host. It also helps to develop immunological memory through an adaptive immune system whereby the immune system can remember pathogens encountered before [83].

Meanwhile, soluble mediators are involved in immunogenic cell death by stimulating immune system components and inducing an immune response [84]. There are two main types of cancer immunotherapies: passive and active. Passive immunotherapy does not depend on the body's natural immune system to target and kill cancer cells. Still, it utilises immune system components like antibodies produced in a laboratory to identify tumour antigens [85]. In contrast, active immunotherapy stimulates and boosts the immune system to fight against cancer cells. It involves the induction of the host defences towards certain antigens. It can be divided into specific and non-specific. Specific immunotherapies stimulate the immune response against particular tumour cells, while non-specific immunotherapies comprise cytokines and immune adjuvants that enhance the overall host immune system [86].

Previously, cancer immunotherapies were a worry due to their highly toxic properties, low to negligible efficacy, or both. However, there has been some advancement in the immunology of cancer that significantly affects people nowadays [86]. On the other hand, passive cancer treatments are applied to cancer patients with weak, no or low response levels of the immune system [87, 88]. Figure 4 indicates the differences between active and passive immunotherapy [89].

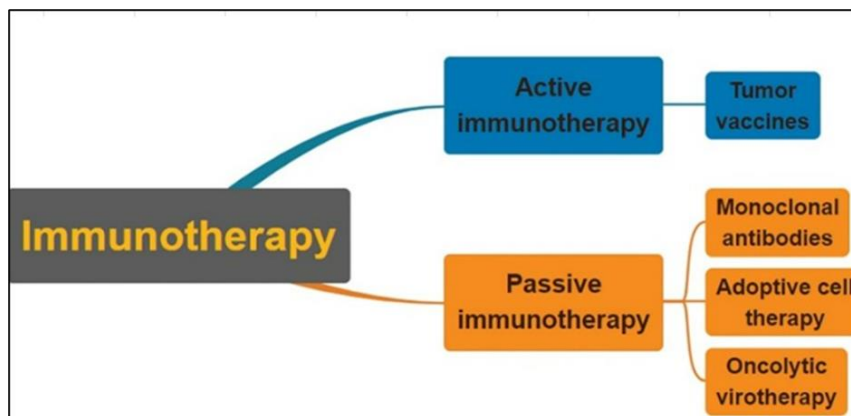


Figure 2. Active and passive immunotherapy.

3.13. Potential of the Studied Compounds as Cancer Immunotherapies

It was estimated that 30% to 90% of cancer patients took some form of supplements and micronutrients to support immunity and reduce treatment side effects upon being diagnosed with cancer. Patients with micronutrient deficiencies are prone to various infections and even body dysfunctions due to weakened immune responses to pathogens such as viruses like SARS-CoV-2, which causes COVID-19 [90, 91]. With a better understanding of the dynamic interactions between our immune system and cancer development, nutritional immunology—the use of natural compounds as immunomodulators in cancer patients—has begun to emerge [91].

Table 2 summarises the potential of the studied compounds as cancer immunotherapies.

Table 2. The potential of studied compounds as cancer immunotherapies.

Compounds	Findings	References
Astaxanthin	Numerous cancer-preventive and therapeutic compounds have recently been extracted from edible marine organisms. Astaxanthin, a xanthophyll red-coloured carotenoid, displayed different biological activities, including anti-inflammatory, antioxidant, proapoptotic, and anti-cancer effects. It can induce apoptosis by downregulating antiapoptotic protein (Bcl-2, p-Bad, and survivin) expression and upregulating proapoptotic ones (Bax/Bad and PARP). These mechanisms can exert anti-cancer effects on colorectal cancer, melanoma, or gastric carcinoma cell lines. Moreover, it possesses antiproliferative activity in many experimental models and enhances the effectiveness of conventional chemotherapeutic drugs on tumour cells, underling its potential future use.	Dyshlovoy [92] and Faraone, et al. [93]
Tocotrienols	Apoptosis is a critical process used as an innate defence mechanism against cancer initiation. Several in vitro and in vivo experiments have confirmed natural molecules' apoptosis-inducing potential. Tocotrienols are among several natural compounds with effective antitumor activity via apoptosis-inducing pathways. Increasing lines of evidence have ascertained that the anti-cancer activity of T3 was primarily mediated by inhibiting two essential transcription factors, NF-κB and STAT3 and their regulated gene products. For example, T3 was shown to inhibit the tumour necrosis factor-alpha (TNF-α)-induced NF-κB activation, which resulted in the downregulation of its related gene products that are involved in cell survival, including inhibitors of apoptosis proteins (IAP)-1, -2, B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL),	Hayes [81]; Stanculeanu, et al. [82]; Aggarwal, et al. [94] and Constantinou, et al. [95]

Compounds	Findings	References
	cellular FLICE-like inhibitory protein (cFLIP), X-linked inhibitor of apoptosis (XIAP), survivin etc. Moreover, T3 inhibited Src kinase, Janus kinase (JAK) 1, and JAK2, which are the regulators of STAT3, thus eventually downregulating STAT3.	
Tocopherols	Vitamin E is a potential candidate due to its safety. Accumulating evidence on the anti-cancer potency of vitamin E has shifted the focus from tocopherols (TOCs) to tocotrienols (TTs). γ -TT and δ -TT have the highest anti-cancer activities and target common molecular pathways involved in inhibiting the cell cycle, the induction of apoptosis and autophagy, and inhibiting invasion, metastasis, and angiogenesis.	de Camargo, et al. [16]; Absalome, et al. [17] and Constantinou, et al. [95]
Fucoxanthin	PI3K/AKT/NF- κ B is a classic signal transduction pathway in cells. The activation of PI3K/AKT/NF- κ B signalling pathway can promote the expression of EMT-related transcription factors, such as Snail and Twist, which contributes to lung cancer proliferation and metastasis. Using western blotting, the work tested the effect of FX on the PI3K/AKT/NF- κ B signalling pathway in human lung cancer cells. The results demonstrated that the expressions of PI3K, p-AKT and NF- κ B p65 were significantly decreased to 73.77%, 47.26% and 76.56%, respectively, in A549 cells, 17.26%, 26.37% and 25.6% in H1299 cells, 47.86%, 67% and 45.48% in H446 cells after FX treatment for 48 h. FX can inhibit PI3K/AKT/NF- κ B signalling pathway in human lung cancer cells.	Ming, et al. [96]
Beta-carotene	Several years ago, some researchers conducted in vitro experiments using beta-carotene and gastric cancer cells, indicating that beta-carotene mainly fights gastric cancer cells through apoptosis, cell signal transduction and oxidative stress.	Chen, et al. [97]

4. CONCLUSION

All in all, the current work has discovered astaxanthin, tocotrienols and tocopherol's anti-inflammatory properties and antioxidant properties of beta-carotene and fucoxanthin. It could be noted that natural astaxanthin extracted mainly from *H. pluvialis*, tocopherols, and tocotrienols extracted from palm oil have the potential to treat inflammation by reducing or downregulating pro-inflammatory markers. The ability to downregulate the pro-inflammatory markers has made these compounds potential candidates to be utilised as therapeutic agents for SARS-CoV-2 infection. When SARS-CoV-2 infects humans, it is reported that several pro-inflammatory markers, including IL-1, IL-6, IL-12, and TNF α , will be upregulated. It is believed that when these compounds were applied to SARS-CoV-2 infected cells, the upregulated pro-inflammatory markers would be downregulated, thus alleviating the inflammation. Nevertheless, more studies on the potential of these compounds to reduce the inflammation caused by SARS-CoV-2 should be conducted. Also, the potential combination of these compounds should be further evaluated. Apart from that, the antioxidant properties of fucoxanthin, mainly extracted from *P. tricornutum* and beta-carotene from *D. salina*, have been proven to treat several medical complications, including hypertension, obesity, type-2 diabetes, osteoporosis, and heart disease. Fucoxanthin and beta-carotene's ability to mitigate chronic diseases align with achieving a healthy community. On the other note, the studied compounds have a growing potential to be utilised as cancer immunotherapies as these compounds have been proven to exert anti-cancer properties, as described in previous studies. The studied anti-inflammatory compounds could manage the inflammation caused by SARS-CoV-2 infection, while the antioxidant compounds could treat chronic diseases. Also, all the studied compounds could be utilised as cancer immunotherapies. Using these compounds as potential therapeutic agents and supplementations could lead to the successful implementation of the health community concept.

ABBREVIATIONS

AA: Arachidonic Acid; ACE-2: Angiotensin II; AD: Alzheimer's Disease; AIDS: Acquired Immunodeficiency Syndrome; ARD: Acute Respiratory Distress; CAT: Catalase; COX: Cyclo-oxygenase; CRP: C-reactive protein;

CVD: Cardiovascular Disease; cyPGs: Cyclopentenone Prostaglandins; DED: Dry Eye Disease; DKD: Diabetic Kidney Disease; DNA: Deoxyribonucleic Acid; EFAs: Essent Fatty Acids; FDA: Food and Drug administration; FO: Fish Oil; GPx: Glutathione Enzymes ; GR: Glutathione Reductase; HCC: Hepatocellular Carcinoma; HDL: High-density Lipoprotein; HMGB1 : High-mobility Group Box 1 (HMGB1); IFALD: Intestinal Failure-Associated Liver Disease; IFN: Interferons; II: Intravenous immunoglobulin; IL : Interleukin; ILEs: Lipid Emulsions; iNOS: Inducible Nitric Oxide Synthase; LDL: Low-density Lipoprotein; LOX: Lipoxxygenase; LPO : Lipid Peroxidation; LTs: LOX Synthesises Leukotrienes; MCTs: Medium-chain Triglycerides; MPPs: Matrix Metalloproteinases; NAT-AX: Natural Astaxanthin; NO: Nitric Oxide; PGs: Prostaglandins; PH-AX: Phaffia Astaxanthin; PKC: Protein Kinase-C; PLA2: Phospholipase A2; PMNs: Polymorphonuclear Neutrophils; PN: Parenteral Nutritions; PPAR: Proliferator-activated Receptor; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; RRR: Natural Source; SARS: Severe Acute Respiratory Syndrome; SOD: Superoxide Dismutase; SPI: Soy Protein Isolate; SYN-AX: Synthetic Astaxanthin; TGF- β : Transforming Growth Factor- β ; TXA2: Thromboxane A2; VA: Vitamin A; VE: Vitamin E; WHO: World Health Organization; α -TOH: alpha-tocopherol.

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