# KORESPONDENSI PAPER

JUDUL : **Critical review on the immunomodulatory activities of carrot's β-carotene and other bioactive compounds**

JURNAL : **Journal of Functional Foods**

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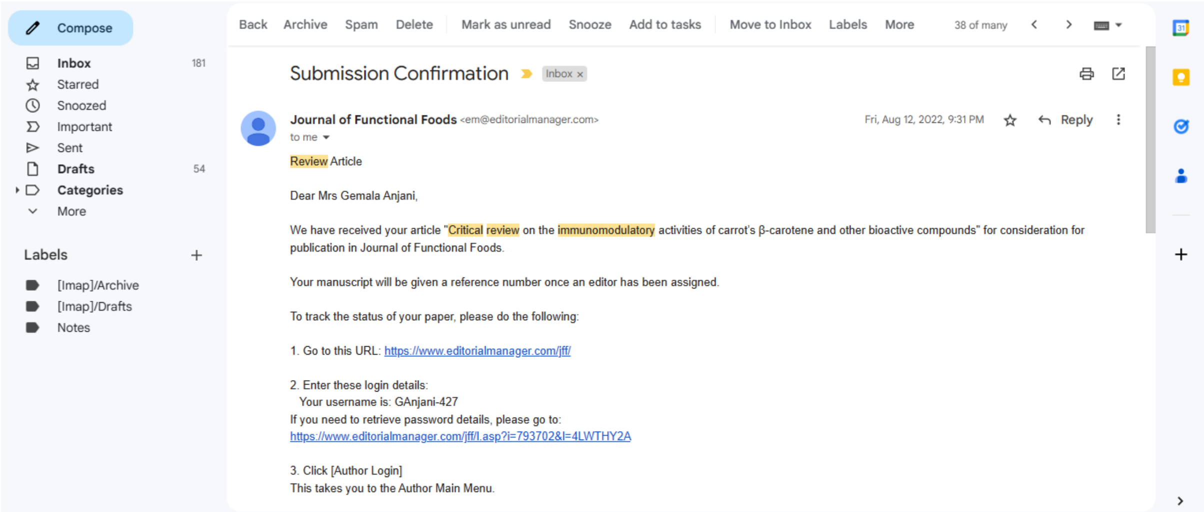
# Submission Artikel



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Ms. Ref. No.: JFF-D-22-00939
Title: Critical review on the immunomodulatory activities of carrot's β-carotene and other bioactive compounds
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Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

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- The abstract should not exceed 150 words. It should state briefly the purpose of the research, methods, the principal results, and major conclusions. There are two different abstracts in the present paper. They should be made one within 150 words.
- Abbreviations must be defined at their first mention (abstract and text separately).
- The reference style of the present paper is not followed by that of Journal of Functional Foods.
- In the revised version, all the corrected and new parts should be highlighted (in red color for example) in order to be checked by reviewers and editor.

Reviewer #1: Anjani et. al. review the biological functions related to immune regulation of the compounds in carrot, represented by beta-carotene. I appreciate the authors' contribution in this field, your article comprehensively summarizes the reports on functional compounds in carrot. However, I do have some concerns.

Abstract:
Author need to show other compounds except beta-carotene in abstract, eg. phenolic acid and flavonoid, because they also occupy a large part in the paper.

Introduction:
I appreciate the author use COVID-19 to introduce this paper, while, immune advantages shaped by nutrition do not just benefit the one common disease. I suggest that author supplement more cases and reduce COVID-19.

From "Nutrition and bioactive contents" to "Other bioactive compounds":
These sections are summarized very well. However, this part is more like a "summary" than a review. To be sure, an excellent review is not summary sentences + a bunch of reports, it should link existing reports well in logically and bring us new informations or inferences. Table 2 and Fig. 2 are very good.

Challenges and future development:
I suggest that this part is not far-reaching enough to guide future work.

Specific comments:
Page 6 line 2 in the pdf file for peer view, β-cartene, B-cartene, β cartene, please check.
Page 13 line 41"naeonate"?, Page 19 line 7 "NFκB", Page 14 line 36 should be"compunds", please check for typos, abbreviation rules and grammar throughout the paper.

Reviewer #2:
The paper is good to be published as it is.

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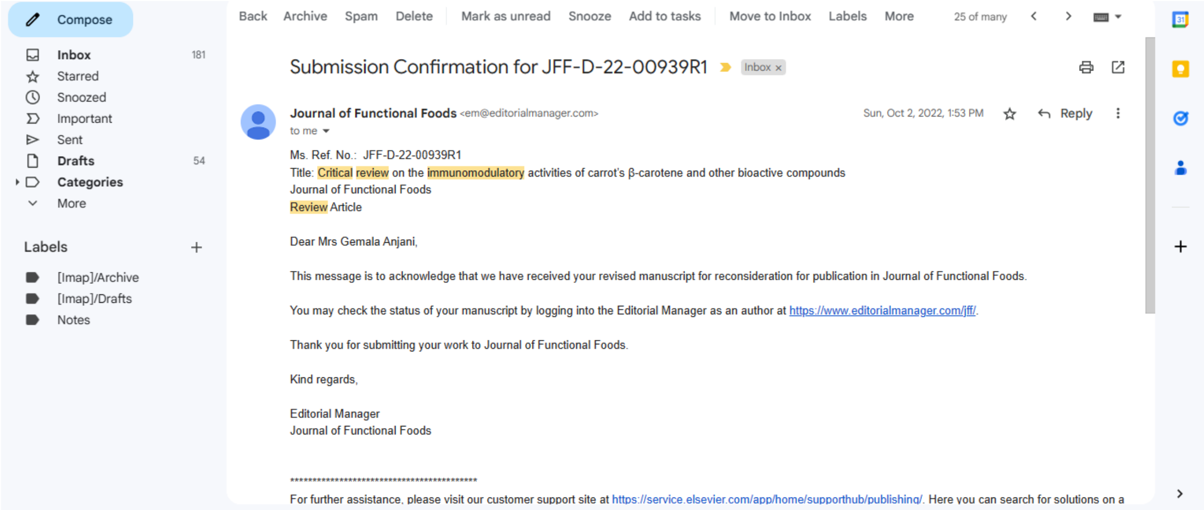

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Title: Critical review on the immunomodulatory activities of carrot's β-carotene and other bioactive compounds
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**Critical review on the immunomodulatory activities of carrot's β-carotene and other bioactive compounds**

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## Abstract

Carrots (*Daucus carota* L.) are vegetables proven to have nutraceutical effects and beneficial for health due to its natural bioactive substances. One of the potential of carrots to maintain optimum health status is by regulating immune response. This literature review summarized the proposed immunomodulatory mechanisms of the antioxidant properties of carrot's β-carotene and other bioactive compounds such as phenolic acid, flavonoid, polyacetylene and ascorbic acid via the anti-inflammatory, antioxidant and overall (innate and adaptive) immune response modulation. Overall, carrot's bioactive compounds regulated pro-inflammatory and anti-inflammatory cytokines, reduced oxidative stress by decreasing the reactive oxygen species accumulation and improving antioxidant capacity and the expression of genes in order to prevent more damaging oxidative destruction. Carrots also modulated the overall immune response by regulating leukocytes, antigens, immunoglobulins, and histamine levels. Thus, the immunomodulatory activity makes carrots as a functional food source that has the potential to prevent and treat various diseases.

## 1. Introduction

The immune system system is critical to the body's physiological and immunological function, therefore any disturbance in the immune system can lead to various diseases (Agita & Thaha, 2017; Coussens & Werb, 2002). The immune is a complex framework designed primarily of leukocytes and various immune components such as antibodies, proteins, and cytokines that act as the first defense mechanism against numerous harmful substances in the environment. This interplay of diverse immune components facilitates the establishment of an optimum immune response (Delves & Roitt, 2000). The immune system identifies and eliminates pathogens while inducing inflammation, cell or tissue damage, cell death, and wound healing in order to preserve redox balance in immune cells in order to prevent various disorders. If homeostasis is not maintained, immune-mediated diseases, metabolic disorders, and inflammatory diseases will develop, as well as susceptibily to infectious diseases such as COVID-19 (Adapa et al., 2011; Q. Li et al., 2022; Nardy et al., 2015; Paragh et al., 2014).

Nutrition is one of the factors that influences the immune system. For instance, nutritional deficit may result in decreased immune responses, and supplementation of those specific components would often restore the compromised immune responses (Venter et al., 2020) . Optimal nutrition intake affects the immune response through regulating various genes expression and signaling molecules (Farhan Aslam et al., 2017). Immunomodulators are components that regulate the body's immune system (Venkatalakshmi et al., 2016). Immunomodulators are not only available in endogenous form, but also from exogenous sources whose mechanism of action is often based on antioxidant properties. Studies have been able to prove that some natural antioxidants from plants can act as natural immunomodulators. Immunomodulators from antioxidant source maintain health status through regulation of the oxidant-antioxidant balance and immune response. Antioxidants operate either directly or indirectly, by eliminating reactive oxygen-nitrogen species or enhancing the body's antioxidant balance, so that immune and inflammatory responses may be regulated (Ortuño-Sahagún et al., 2017).

Currently, many bioactive compounds from plants have been investigated for their potential benefits as immunomodulators (Venkatalakshmi et al., 2016). Turmeric, Echinacea, green tea, and chili pepper are examples of plant sources with immunomodulatory effects (Catanzaro et al., 2018; Grüter et al., 2020; Hasan et al., 2021; Rahayu et al., 2018). However, intake from some of these sources are still limited. Carrots *(Daucus carota* L.) are beneficial vegetables in the world due to its massive production and its usage as food for public daily intake, both in fresh and processed form. This vegetable has nutraceutical effects and is beneficial for health due to its high natural bioactive substances (Ahmad et al., 2019).

Carrots' main carotenoid is β-carotene, a well-known and extensively researched carotenoid. Carotenoids are phytonutrients that give fruits and vegetables their unique yellow, orange, and red hues. β-carotene provides a variety of health benefits in addition to providing color in food. It has a high antioxidant capacity and provides a number of health advantages, including decreasing the risk of certain illnesses and cancers, strengthening the immune system, and protecting against age-related eye degeneration (Gul et al., 2015).

A recent review has shown that carrots act as antioxidants, antidiabetic, antimicrobial, nephroprotective, hepatoprotective, cardioprotective, anti-inflammatory and wound healing properties (Al-Snafi, 2017). Moreover, carrots can also improve the immune system and eye health (da Silva Dias, 2014; Mahammad Shakheel B et al., 2017). The previous review examined the protective effect of β-carotene against gastric cancer based on epidemiological surveys (Chen et al., 2021). In addition, β-carotene also plays a role in stimulating lipid catabolism, which metabolizes lipids, which is one of the atherosclerotic factors of cardiovascular disease (ASCVD) (Miller et al., 2020).

Although prior review have addressed the health benefits of carrot bioactive compounds (da Silva Dias, 2014), especially β-carotene, the specific immunomodulatory activities have not been well investigated as the mechanism is known to be exceedingly complicated and remain unclear. An experimental research discovered that administration of carrot juice improved antioxidant capacity and decreased malondialdehyde after 3 months consumption of carrot juice (Potter et al., 2011). A randomized cross-over study also noted an improvement in interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α) in healthy men after consumption of carrot juice or tomato juice in healthy men after conducting 2-weeks low carotenoid periods (Watzl et al., 2003). Therefore, the purpose of this literature review is to explore into the potential immunomodulatory mechanism of carrots' β-carotene and its other bioactive compound.

## 2. Immunomodulator

Immunomodulator is defined as substance that modulate the immunological response, either decreasing the immune response as a type of therapy for autoimmune diseases or enhancing the immune response to immuno-compromised conditions (Ilyas et al., 2016). Immune system is defined as the body's natural defense system against disease and disorders (Sharma et al., 2017). The immune system is divided into innate and adaptive immune systems, both of which determine a person's ability to fight harmful agents. Innate immunity is known as the first defense against pathogens and consists of epithelial protection, antimicrobial proteins and peptides, humoral and cellular components. Then, the adaptive immune system was activated by the innate immune systems, which contributed in the foreign antigen recognitions (Tyagi, 2016). The adaptive immune responses consist of B lymphocytes with antigens, T lymphocytes and regulatory T cells (Treg) (Sharpe & Mount, 2015).

The main source of cytokines in the body is the T lymphocytes, in which these cells have specific antigen receptors that enable pathogen recognitions. T lymphocytes expressing the CD4 are known as T helper (Th) cells. This subset is further subdivided into Th1 and Th2 cells, which produce Th1 and Th2 cytokines, respectively. Th1 cytokines tend to act as pro-inflammatory agents for intracellular pathogens elimination. Th1 cytokines include TNF-α, interferon gamma (IFN-γ), IL-1β, IL-2 and IL-18. Th2 cytokines, on the other hand, are known to be more complex. Th2 cytokines include the immunoglobulin response-related cytokines such as IL-4, IL-5, IL-9, and IL-13, as well as pro-inflammatory IL-6 and anti-inflammatory IL-10. As a result, a balance of Th1 and Th2 responses is required in order to combat pathogens effectively while avoiding uncontrollable inflammation (Berger, 2000).

Inflammation is known as a normal physiological response of the body's immune system to counter harmful stimuli such as infections, damaged cells and toxic compounds. These factors can trigger an acute or chronic inflammatory response in the heart, pancreas, liver, kidneys, lungs, brain, gastrointestinal tract, and reproductive system, which can lead to tissue damage or diseases. Infectious and non-infectious agents, as well as cell damage, usually activate inflammatory signaling pathways such as nuclear factor kappa-B (NFκB), mitogen-activated protein kinases (MAPK), and janus kinase-signal transducer and activator of transcription (JAK-STAT) (Chen et al., 2018). Excessive inflammation exacerbates functional disorders and tissue injuries (Bartold & Dyke, 2017). For instance, the hyper-inflammation that occurs in COVID-19 causes a "cytokine storm" leading to acute respiratory distress syndrome (ARDS), pneumonia, organ failures, fibrosis, or even death (Channappanavar & Perlman, 2017; Shi et al., 2020).

During the homeostatic state, several endogenous and external factors contribute to immunosuppression and immuno-stimulation (Jantan et al., 2015), thus affecting the innate and adaptive immune response (Fig. 1). Immune response modulation occurred to regulate the body's immune response in therapeutic and preventive attempts against causative agents (Rasheed et al., 2016; Razali et al., 2016). The use of immunomodulators is presently one of the most pressing issues in the treatment of numerous diseases (Sharma et al., 2015).

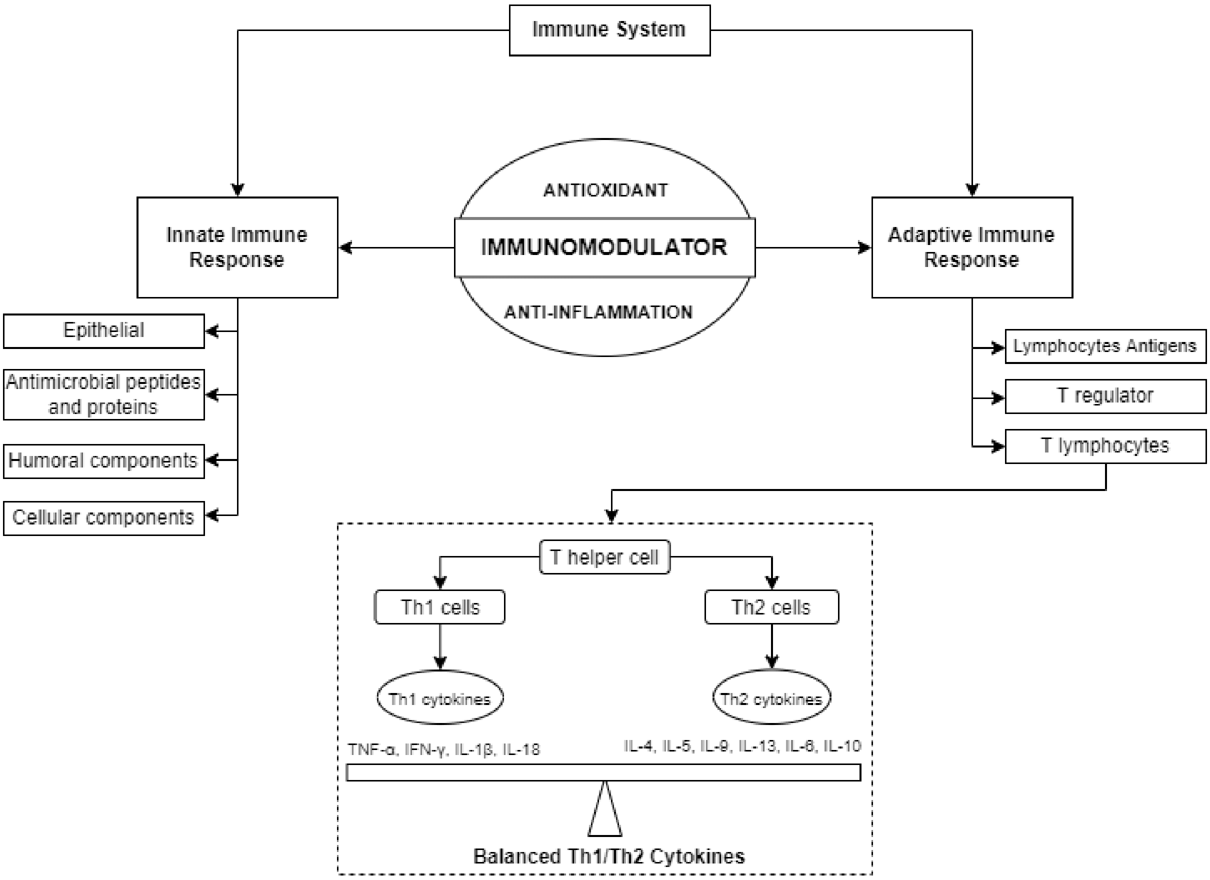



Figure 1. Immunomodulator Mechanism via Antioxidant and Anti-Inflammation Properties. Th1, T helper type 1; Th2, T helper type 2; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; IL, interleukin.

Application of plant-derived bioactive compounds has become one of the primary areas of exploration for the natural immunomodulators (Shukla et al., 2014). The use of natural immunomodulators is currently increasingly being accepted in the world because of their wide range in preventing and treating disease via changes in immune response or oxidant-antioxidant status (Ajith et al., 2017).

The antioxidant defense system involves free radical reduction, antioxidant enzyme activation and maintenance, enhancement of other antioxidant mechanisms, and specific immunomodulatory effects (Ajith et al., 2017). Plants that serve as natural immunomodulators have the capacity to boost immunity by activating innate immune responses such as activating immune cellular components, modifying cytokine profiles, decreasing infection and inflammation. The immunomodulatory properties of these plants cannot be separated from their bioactive compounds (Jantan et al., 2015).

## 3. Nutrition and bioactive contents of carrots

*Daucus carota* L., or commonly known as carrot, is a vegetable belonging to the *Apiaceae* family (Bussmann et al., 2020). Based on FAOSTAT 2021 data from the Food and Agriculture Organization (FAO), in 2019, nearly 44.8 million tons of carrots and radishes were widely produced for daily consumption (FAOSTAT, 2021). Carrots consist of stems and roots in which the roots consist of the periderm, outer cortex (phloem) and nucleus (xylem). The part of the carrot that is commonly consumed is the root. High quality carrots have a greater proportion of phloem than xylem (Char, 2018). The taxonomy of carrots from the Integrated Taxonomic Information System database are as follows:

Kingdom : *Plantae*
Sub Kingdom : *Viridiplantae*
Division : *Tracheophyta*
Sub Division : *Spermatophytina*
Class : *Magnoliopsida*
Order : *Apiales*
Family : *Apiaceae*
Genus : *Daucus* L.
Species : *Daucus carota* L.

Orange carrots are the dominant type of carrots and are mostly used in various cuisines both fresh or cooked. The rate of carrot consumption increased due to an increase in public awareness of carrots as functional food that is useful in supporting healthy lifestyle (Ergun, 2018). The antioxidant activity of orange carrots based on the Ferric Reducing Antioxidant Power method (FRAP), 2,2′-Azinobis-(3-Ethylbenzthiazolin-6-Sulfonic Acid) (ABTS) and Cupric Reducing Antioxidant Capacity (CUPRAC) were 1.22 mol TE/g, 1.22 mol TE/g and 3.07 mol TE/g fresh weight, respectively (Singh et al., 2018). The following Table 1 presents data on the nutritional and bioactive content of carrots .

Table 1. Nutrition and Bioactive Contents in Carrots (per 100 g FW)

| **Component** | **Amounts** | **Unit** | **Reference** | **RDA (age 10-12 y.o)** |
|---|---|---|---|---|
| Energy | 41 | kcal | USDA, 2015 | 2.05% |
| Proximate | | | | |
| Moisture | 88,3 | g | USDA, 2015 | 4,77% |
| Carbohydrate | 9,58 | g | USDA, 2015 | 3,19% |
| Protein | 0,93 | g | USDA, 2015 | 1.86% |
| Fat | 0,24 | g | USDA, 2015 | 0,37% |
| Fibre | 2,80 | g | USDA, 2015 | 10% |
| Ash | 0,97 | g | USDA, 2015 | 4,77% |
| Iron | 0,3 | mg | USDA, 2015 | 3.75% |
| Magnesium | 12 | mg | USDA, 2015 | 7.5% |
| Phosphorus | 35 | mg | USDA, 2015 | 2.8% |
| Potassium | 320 | mg | USDA, 2015 | 8.21% |
| Sodium | 69 | mg | USDA, 2015 | 3.63% |
| Calcium | 33 | mg | USDA, 2015 | 2.75% |
| Zinc | 0,24 | mg | USDA, 2015 | 3% |
| Manganese | 0,14 | mg | USDA, 2015 | 26,6% |
| Vitamin B2 | 0,06 | mg | USDA, 2015 | 4.61% |
| Vitamin B3 | 0,98 | mg | USDA, 2015 | 8.17% |
| Folate | 19 | µg | USDA, 2015 | 4.75% |
| Vitamin C | 5,90 | mg | USDA, 2015 | 11.8% |
| Total Flavonoid | 4,50 | mg | Bahorun et al., 2004 | - |
| Quercetin | 1,50 | mg | Bahorun et al., 2004 | - |
| Luteolin | 0,80 | mg | Bahorun et al., 2004 | - |
| Kaempferol | 0,60 | mg | Bahorun et al., 2004 | - |
| Total Phenolic | 89,30 | mg | Hellström et al., 2020 | - |
| Caffeic acid | 41,10 | mg | Hellström et al., 2020 | - |
| Ferulic acid | 7,10 | mg | Hellström et al., 2020 | - |
| p-coumaric acid | 73,10 | µg | Rozan, 2017 | - |
| Carotenoids | 12,71 | mg βCE | Rozan, 2017 | - |
| α-carotene | 3,38 | mg | Rozan, 2017 | - |
| β-carotene | 8,21 | mg | Rozan, 2017 | - |

| | | | | |
|---|---|---|---|---|
| *Falcarinol* | 359 -1900 | µg | Rawson et al., 2010 | - |
| *Falcarnidiol* | 154-18000 | µg | Acworth et al., 2011 | - |
| *Falcarni-acetate* | 77-140 | µg | Acworth et al., 2011 | - |

## 4. Potential of carrots as immunomodulator

Carrots and their phytochemical compounds have been shown to have potential as a natural immunomodulator through both antioxidant and anti-inflammation properties, or by their modulation to other immune components (Table 2). For example, Roselli et al. (2012) indicated that organic carrot consumption at a rate of 70 mg/kg of feed for 30 days stimulated intestinal and peripheral immunity, with an increase in lymphocytes, including regulatory T cells (Treg). Saba et al. (2019) showed an improvement in superoxide dismutase (SOD) after administration of carrot extract at the dose of 500 mg/kg for 7 days in oxidative stress rats model. SOD regulates extracellular reactive oxigen species (ROS) and protects tissues from damage, as it is well recognized that while ROS are necessary during the immune response to pathogens, they also cause collateral tissue damage (Break et al., 2012). In a cytotoxic oxidative tissue damage model, Embugushiki et al. (2013) also observed an improvement in the activity of antioxidant enzymes after 5 days of carrot juice intervention (as drinking water). As previously stated, increasing the body's antioxidant status by administrating natural antioxidant counteracts the impacts of inflammation and further tissue injury through improvement of oxidative stress (Arulselvan et al., 2016).

The body is constantly in a condition of equilibrium between the formation and elimination of free radicals. The endogenous antioxidant defense mechanism against free radicals consists of antioxidant enzymes (catalase, glutathione reductase, and SOD), as well as glutathione, urate, coenzyme Q, or exogenous stimuli including bioactive compounds such as β-carotene. The immune system's function of combating infections is one source of ROS generation, because neutrophils produce free radicals. Micronutrient deficiency is known to cause a deterioration in immune function, both innate and adaptive, thereby rendering the body susceptible to pathogen attack as a consequence of immune imbalance. Thus, it is critical to consume bioactive compounds that serve as antioxidants in order to maintain a balanced immune response (Brambilla et al., 2008).

Carrots contain a variety of bioactive compounds, including flavonoids, phenolic acids, carotenoids, polyacetylene, and ascorbic acid. Those bioactive compound was shown to have immunomodulatory properties due to their antioxidant, anti-inflammatory, and regulatory properties of innate and adaptive immune response components. These modulatory activities included the suppression and stimulation of inflammatory cytokines, antioxidative activity through ROS scavenging activity and improvement in endogenous antioxidant defense, as well as modulating pro-inflammatory and anti-inflammatory signaling pathways (Fig. 2).

Carotenoids are isoprenoids present in a variety of plants, including carrots. Carotenoids are acyclic molecules with five to six C rings at one or both ends (Sharma et al., 2012). Carotenoids' color variation is caused by conjugated double bonds in polyene chains that function as chromophore (Rodriguez-Concepcion & Stange, 2013; Ruiz-Sola & Rodríguez-Concepción, 2012). The main carotenoids present in orange carrots are α-carotene and β-carotene (Søltoft et al., 2011).

β-carotene is a secondary metabolite produced by plants that belongs to the non-oxidized carotenoids group. β-carotene possesses a long chain of conjugated double bonds due to its role as a polyene compound of the derived acyclic structure (Fratianni et al., 2010; Meléndez-Martínez et al., 2010). Carotenoids, which have the same structure as retinol molecules, exhibit vitamin A activity, with β-carotene having the highest bioactivity as a vitamin A precursor. It is the most potent vitamin A precursor and occurs naturally as a combination of several isomers (cis and trans) of the β-carotene molecule (Toti et al., 2018). *In vivo* model indicated that long-term consumption of β-carotene reduced the production of malondialdehyde (MDA), the end product of lipid peroxidation (Hosseini et al., 2010).

Table 2. The Roles of Carrot and its bioactive compound as immunomodulator

| Subjects | Study Design | Preparation | Dose | Route | Duration | Immunomodulatory Activity | Modulation | Parameters/Mediator Affected | Ref |
|---|---|---|---|---|---|---|---|---|---|
| BALB/c mice | *In vivo* | Organic and conventional carrots | 70 g/kg of feed | Oral | 30 days | immunostimulant in intestinal and peripheral immunity | ↑ | Lymphocyte population, including Treg | Roselli et al., (2012) |
| APAP-induced oxidative stress BALB/c mice | *In vivo* | Carrot deuterium-depleted aqueous extract | 500 mg/kg | Oral | 7 days | Oxidative stress indicators | ↓ | ALT, AST and 8-OHdG | Saba et al., (2019) |
| | | | | | | Antioxidant enzyme | ↑ | SOD | |
| Cadmium-induced oxidative cytotoxic damage in rats | *In vivo* | Carrot juice | *ad libitum* | Oral | 5 days | Improve endogenous antioxidant | ↑ | Catalase, SOD, GPx | Embugushiki et al., (2013) |
| High fructose diet-induced inflammation in weaning wistar rats | *In vivo* | Carrot juice | 0.6 mL | Oral | 8 weeks | Pro-inflammatory mediator | ↓ | MCP1 and hsCRP | Mahesh et al., (2017) |
| LPS-induced CB57BL/6 mice | *In vivo* | Carrot's falcarinol | 5 mg/kgBW | Oral | 7 days | Immune homeostasis's regulator | ↑ | Heme oxygenase-1 8.42 times in mRNA levels and 10.7 times in protein levels | Stefanson & Bakovic, (2020) |
| | | | | | | Cytokine release | ↑ | Plasma IL-4, IL-9, IL-10, IL-13, illustrating the characteristics in the improvement of type 1 inflammation | |
| LPS-induced CB57BL/6 mice | *In vivo* | Carrot's falcarinol | 5 mg/kgBW | Oral | 7 days | Pro-inflammatory cytokines | ↓ | IL-6, TNF-α/TNF-αr, and IFNγ gene expression | Stefanson & Bakovic, (2018) |
| Albino wistar rats | *In vivo* | Carotenoid extract from carrots | 559 mg/kg | Oral | 21 days | White blood cells | ↑ | lymphocytes, eosinophils, monocyte counts | Ekam et al., (2006) |

↓, decrease; ↑, increase; APAP, Acetaminophen; LPS, lipopolisaccharide; Treg, T regulator; SOD, superoxide dismutase; GPx, glutathione peroxidase; MCP-1, monocyte chemoattractant protein-1; hsCRP, high-sensitivity C-reactive protein; ALT, alanine transaminase; AST, aspartate transaminase; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

MDA is an oxidative stress biomarker that contributes to maintain the balance of physiological functions, including innate and adaptive immune responses, thus affecting pathological settings such as neurodegenerative diseases, metabolic diseases, cancers and also infectious diseases (Papac-Milicevic et al., 2016). For instance, in some autoimmune disorders, such as systemic lupus erythematosus (SLE), MDA levels are elevated due to metabolic dysregulation and increased ROS. Suppressing excess MDA in interventions is therefore advantageous (Hardt et al., 2018).

### 4.1. Immunomodulatory effect of β-carotene

Katsuura et al. (2009) showed that β-carotene administration in a time and dose-dependent manner was positively correlated with lipid peroxidation and glutathione synthesis, as well as negatively correlated with the transcription of cytokines such as IL-1b, IL-6, and IL-12 p40, in lipopoliscaccharide (LPS) and INF-gamma-induced RAW264 cells. This indicated that β-carotene triggers changes in intracellular redox status thereby regulating the immune function of macrophages.

Monocyte chemoattractant protein-1 (MCP-1) is a CC-chemokine that plays an important role in the inflammatory process by attracting or increasing the expression of inflammatory factors/cells. MCP-1 is involved in the pathogenesis of a variety of diseases, both directly and indirectly, including COVID-19, cancer, neuroinflammatory diseases, rheumatoid arthritis, and cardiovascular disease (Deshmane et al., 2009). In high-fructose diet-induced weaning rats, Mahesh et al. (2017) demonstrated that 0.3 mL of β-carotene from carrot juice reduced the level of free fatty acid (FFA), MCP-1 and high-sensitivity C-reactive protein (hsCRP) by 50%, 32% and 40% respectively. Ekam et al., (2006) analyzed the immunomodulatory effect of carotenoid extracts (α-carotene and β-carotene) of carrots at a dose of 559 mg/kg for 21 days, increased levels of lymphocytes, eosinophils, monocytes and platelets in male Wistar rats was observed.

In their investigation on weanling mice, Nishida et al. (2014) discovered that β-carotene supplementation at a dose of 50 mg/kg feed for 14 weeks elevated the synthesis of immunoglobulin A (IgA) in the jejunum or ileum. Retinoic acid-mediated immune response was responsible for this outcome. Considering neonate and children are susceptible to diarrhea and gastrointestinal infections, that study also found an improvement in the immune response in the gastrointestinal tract (Nishida et al., 2014). Nishiyama et al. (2011) investigated the effect of β-carotene supplementation in pregnant mice during pregnancy and lactation on IgA parameters from mammary glands, guts, and transfer of IgA from milk to neonate mice. Administration of 50 mg/kg of β-carotene supplements from 6.5 days postcoitus to 14 days postpartum showed an increased presence of IgA in the mammary glands and ileum during lactation, thereby triggering increased transfer of maternal milk IgA to neonate mice. IgA is the most abundant type of antibody in the body, and it protects mucous glands from microbial invasion while also maintaining immune homeostasis in the gastrointestinal, respiratory, and vaginal tracts. The relevance of IgA is proven by the protective immune response against intestinal viral enteropathogens depends on the presence of IgA (Blutt et al., 2012).

The JAK-STAT pathway is critical in combating the immune system's challenges, extending from infection prevention to cancer protection. This function, however, must be maintained. Excessive and prolonged JAK-STAT signalling is a characteristic that occurs in practically all types of autoimmune disorders (Villarino et al., 2015)**,** as well as arthritis, Alzheimer disease, and osteosarcoma (Chiba et al., 2009; Saravanan et al., 2014; Yan et al., 2015). Signal transducer and activator of transcription 3 (STAT3), specifically, also contributes in the development of inflammatory disease such as periodontitis and other cancer (De Souza et al., 2011; Geiger et al., 2016)**.** One of the primary functions of the jun N-terminal kinase

(JNK)/p38 MAPK is to regulate the immune response, particularly in activating stress. Therefore, pharmacological interventions capable of inhibiting these pathways have been shown to be effective in alleviating inflammation in the diseases mentioned (Jeffrey et al., 2007; Kumar et al., 2003; Manning & Davis, 2003). Yang et al. (2021) showed that administration of β-carotene for 7 days remarkably reduced production of nitric oxide (NO), prostaglandin E2 (PGE2), TNF-α, and IL-1β in LPS-induced intestinal inflammation. Moreover, there was suppression of mRNA expression of IL-1β and TNF-α was observed after intervention. The postulated mechanisms for these findings included autophagy regulation as well as JAK2/STAT3 and JNK/p38 MAPK inflammatory pathways.

According to a prior review, β-carotene inhibits ROS-mediated inflammatory signaling, including the MAPK pathway and redox-sensitive transcription factors, as well as the production of inflammatory mediators including IL-8, nitric oxide synthase (NOS), and cyclooxygenase-2 (COX2) (Kang & Kim, 2017). The anti-inflammation mechanism of β-carotene was related to the reduction of the NFκB inflammatory pathway and suppression of ROS production (Di Tomo et al., 2012). A variety of inflammatory disorders, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis, atherosclerosis, SLE, type I diabetes, chronic obstructive pulmonary disease, and "cytokine storm" in COVID-19, have been linked to NFκB activation (Hariharan et al., 2021; Pai & Thomas, 2008). Targeting NFκB signaling is a promising method for anti-inflammatory treatment since unregulated NFκB activation is associated in these numerous inflammatory disorders (T. Liu et al., 2017). Zhou et al. (2018) discovered that β-carotene blocked the NFκB activation pathway and diminished the production of pro-inflammatory cytokines. Furthermore, this study revealed that β-carotene treatment markedly reduced oxidative stress by lowering ROS, MDA, and NO while increasing SOD. van Helden et al. (2013) showed a depletion in mRNA expression of pro-inflammatory genes associated with the NFκB pathway involved in the production and regulation of IFN in lungs, liver and adipose tissue in β-carotene 15,15′-monooxygenase 1 knockout (Bcmo1$^{-/-}$) mice after 14 days of β-carotene supplement intervention.

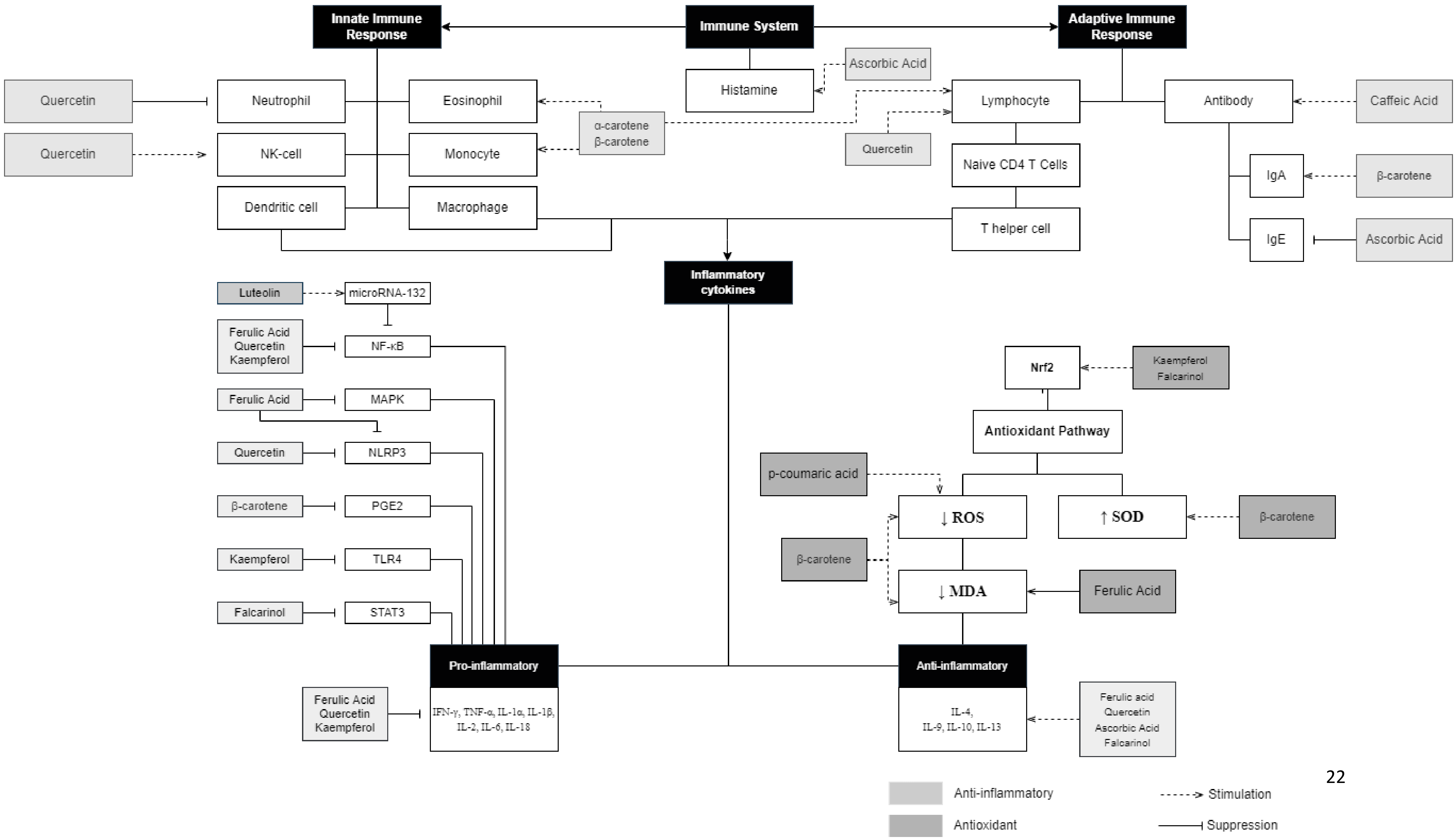
### *4.2. Other Bioactive Compound in Carrots as Immunomodulator*

#### *4.2.1. Phenolic acid and flavonoid*

The most abundant phenolic acid in carrots is chlorogenic acid, such as caffeic, ferulic and p-coumaric acids (Arscott & Tanumihardjo, 2010). Caffeic acid influenced antibody production and inflammatory signaling, improving oxidative state in SARS-CoV-2 infected individuals (Adem et al., 2021). Ferulic acid pre-treatment (50 mg/kg) for 30 days reduced LPS-induced inflammation by upregulating IL-1, IL-6, TNF-α, and IL-10 production. Acute ARDS was improved by ferulic acid's antioxidative and anti-inflammatory effects via inhibition of the MAPK inflammatory pathway, which subsequently resulted in decreased MDA and myeloperoxidase, as well as an increase in antioxidant status (Zhang et al., 2018). Other study had shown that ferulic acid intervention for 4 weeks regulated NFκB pathway at the dose of 40 mg/kg and the inflammasome domain-like receptor family pyrin domain-containing 3 (NLRP3) at the doses of 40 and 80 mg/kg, characterized by decreased levels of TNF-α, IL-1β, and IL-6 mRNA expression in stressed-induced mice (Liu et al., 2017).

The NLRP3 inflammasome, like NFkB, promotes inflammation. NLRP3 alters the immune response or regulates the integrity of intestinal homeostasis in numerous inflammatory disorders such as Alzheimer's, atherosclerosis, atrial fibrillation, osteoarthritis, cancer, and autoimmune diseases such as SLE and IBD (Wang et al., 2020). NLRP3, on the other hand, is vital in viral extermination due to its function in inflammation (Zhao & Zhao, 2020). As a result, modulating these pathways is vital for therapeutic treatment. P-coumaric acid had been shown to ameliorate LPS-induced oxidative damage through ROS scavenging activity and oxidative stress improvement in inflammatory state of the lungs (Kheiry et al., 2020).

The main flavonoids detected in orange carrots were quercetin, luteolin and kaempferol (Bahorun et al., 2004). Quercetin inhibited NFκB and IL-6 signaling, which exhibited an anti-inflammatory impact. The administration of quercetin remarkably reduced LPS-induced lung inflammation, as seen by lower levels of neutrophils, lymphocytes, and pro-inflammatory cytokines in the lungs (Huang et al., 2015). Quercetin also inhibited the activation of the NLRP3 inflammasome, IL-1α, IL-6, and IL-18 secretion (Jiang et al., 2016). Luteolin at a dose of 50 mg/kg reduced TNF-α, IL-1β and IL-6 production (Lodhi et al., 2020). In LPS-induced bronchopneumonia model, luteolin reduces inflammatory injury by regulating the expression of microRNA-132, thereby inhibiting NFκB pathway (Liu & Meng, 2018). microRNA-132 is RNA molecule the involved in the inflammation suppression during wound healing (Li et al., 2015). Kaempferol acted as an anti-inflammatory agent by suppressing the binding of NFκB from DNA decreasing the secretion of pro-inflammatory cytokines, inhibiting toll-like receptor 4 (TLR4) which acted as a trigger in pro-inflammatory response, and increasing expression of nuclear factor target gene mRNA and protein (erythroid-derived 2)-like 2 (Nrf2) which was involved in oxidative damage prevention (Nam et al., 2017; Saw et al., 2014; Tang et al., 2015; R. Zhang et al., 2017). It may be inferred that the majority of these flavonoids and phenolic acids' immunological actions are connected to their anti-inflammatory properties and facilitate the protection of oxidative damage. This is important since many inflammatory and infectious diseases depend on the inflammatory process, as demonstrated by its influence on lung disorders like as ARDS, bronchopneumonia, and lung inflammation.



Immune System
Innate Immune Response
Adaptive Immune Response
Histamine
Ascorbic Acid
Quercetin
Neutrophil
Eosinophil
Quercetin
NK-cell
Monocyte
α-carotene
β-carotene
Dendritic cell
Macrophage
Lymphocyte
Quercetin
Naive CD4 T Cells
T helper cell
Antibody
Caffeic Acid
IgA
β-carotene
IgE
Ascorbic Acid
Inflammatory cytokines
Luteolin
microRNA-132
Ferulic Acid
Quercetin
Kaempferol
NF-κB
Ferulic Acid
MAPK
Quercetin
NLRP3
β-carotene
PGE2
Kaempferol
TLR4
Falcarinol
STAT3
Pro-inflammatory
IFN-γ, TNF-α, IL-1α, IL-1β,
IL-2, IL-6, IL-18
Ferulic Acid
Quercetin
Kaempferol
Nrf2
Kaempferol
Falcarinol
Antioxidant Pathway
p-coumaric acid
↓ ROS
↑ SOD
β-carotene
β-carotene
↓ MDA
Ferulic Acid
Anti-inflammatory
IL-4,
IL-9, IL-10, IL-13
Ferulic acid
Quercetin
Ascorbic Acid
Falcarinol
Anti-inflammatory
Antioxidant
Stimulation
Suppression

Figure 2. Summary of Potential Immunomodulatory Mechanisms of Bioactive Compounds in Carrots. NK-cell, natural killer-cell; CD4, cluster of differentiation 4; IgA, Immunoglobulin A; IgE, Immunoglobulin E; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, *mitogen-activated protein kinase; NLRP3*, NLR family pyrin domain containing 3; PGE2, prostaglandin E2; TLR4, toll-like receptor 4; STAT3, signal transducer and activator of transcription 3; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; IL, interleukin.

*4.2.2. Polyacetylene*

Polyacetylene is a non-volatile phytochemical group consisting of at least two C-C triple bonds. Carrots contain polyacetylene such as falcarinol, falcarindiol, and falcarindiol 3-acetate (Christensen, 2012; Dawid et al., 2015). Recent review showed that polyacetylene has the potential in improving health status due to its antitumor, antifungal, anti-inflammatory, antibacterial and serotogenic properties (Dawid et al., 2015).

The transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) defend against intestinal inflammation and oxidative damage. Falcarinol was shown to be a dietary immunosuppressant in individuals with gastrointestinal inflammation, such as IBD, celiac disease, colitis, and enteritis (Stefanson & Bakovic 2020). Stefanson & Bakovic (2020) proved that falcarinol extract supplementation of 5 mg/kg given twice daily for a week enhanced the heme oxygenase-I (HO-1) expression, which is the target enzyme of Nrf2. This research also observed an increase in IL-4, IL-9, IL-10, and IL-13, indicating a decrease in inflammation after falcarinol ethanolic extracts administration in LPS-induced oxidative stress mice. Stefanson & Bakovic (2018) also demonstrated that pre-treatment of falcarinol extract at a dose of 5 mg/kg twice a day for 7 days prevented pro-inflammatory genes elevation proving its protective effect against systemic and intestinal inflammation in LPS-induced CB57BL/6 mice. That study discovered that LPS induction increased the expression of pro-inflammatory genes such as *IL-6* up to 103.6-fold, *Tnfα* up to 48.8-fold, *Tnfα* receptor (*Tnfαr*) up to 5.1-fold, *Ifnγ* up to 22.3-fold, and STAT3 3.6 times. In the presence of pre-treatment of the falcarinol ethanol extract, the expression level of pro-inflammatory genes (*IL-6*, *Tnfα/Tnfαr* and *Ifnγ*) was equivalent to that of the negative control (not LPS induced), and the expression of STAT3 increased 2-fold. Gastrointestinal inflammation is an important issue because disruption of the gastrointestinal barrier is an indication of early deviations from body's homeostasis state, which lead to the development of more serious and various diseases such as autoimmune, food allergy, obesity, and chronic disorders (Stefanson & Bakovic, 2018). According to the findings of these studies, the potency of falcarinol in alleviating inflammation could be beneficial in the treatment and prevention of diseases in the gastrointestinal tract or other systems.

#### *4.2.3. Ascorbic Acid*

Apart from being rich in provitamin A, carrots also rich in vitamin C (Char, 2018). Vitamin C is a water-soluble vitamin founded in various fruits and vegetables (Devaki & Raveendran, 2017). Vitamin C in carrots is available in the form of ascorbic acid. This vitamin also functions as an antioxidant by scavenging free radicals, thus improving oxidative stress conditions. Vitamin C exerts antioxidative activity by transferring electrons in both enzymatic and non-enzymatic processes to generate less reactive molecules (Akbari et al., 2016).

Ascorbic acid has antiviral properties, and a recent meta-analysis suggested that administering large doses of ascorbic acid relieved common cold symptoms and duration of sickness (Ran et al., 2018). An enhanced immune response and resistance against viral infections by increasing IFN-α/β was observed in the lungs infected with the Influenza A virus in vitamin C deficient mice after the intervention of sodium L-ascorbate (3.3 g/L) for 3 weeks (Kim et al., 2013).

As an antioxidant, ascorbic acid protected lymphocytes from oxidative impairment (Lenton et al., 1999). Supplementation of 1 gram of ascorbic acid for 38 days also decreased the level of IgE and histamine in a swine model induced with soybean glycinin hypersensitivity, indicating a reduce in anaphylactic reactions (Sun et al., 2009). A review summarized another role of ascorbic acid in modulating the immune system is by influencing the functioning and growth of T lymphocytes and NK cells (Van Gorkom et al., 2018). Administration of 100 μM of vitamin C also regulated the cytokines by decreasing IFN-γ and TNF-α, as well as increasing the production of IL-10 in human lymphocytes *in vitro* model (Molina et al., 2014). At 48 and 72 hours after ascorbic acid intervention, splenocytes of C57BL/6 mice induced by LPS or concavalin-A (con-A) showed an upregulation of anti-inflammatory cytokines such as IL-4 and IL-10, as well as downregulation in the expression of pro-inflammatory cytokines such as IL-6, IL-12, and TNF-α, indicating a decrease in pain caused by inflammation (Kong et al., 2015). Mechanism of ascorbic acid in reducing TNF-α and IL-6 production is also involving regulatory effects on the NFκB pathway by suppressing the production and signaling of ROS in NFκB transcription (Bowie & O'Neill, 2000; Cárcamo et al., 2002; Peng et al., 2005).

## 5. Challenges and future development

This review shows the potential of carrot has a huge variety of bioactive compounds that can be used as nutritional/therapeutic agents to modulate the immune system, either on inflammatory processes, antioxidant or redox balance, or on immune components in general. Nowadays, because of the escalating cost of immune therapy, natural medicines produced from plants are becoming more popular. Carrots, in particular, have a significant potential in the prevention or treatment of immune-related disorders due to their widespread availability and low cost. This suggests that developing carrot-based products, such as functional foods or supplements, might be a viable therapy for various immune-mediated diseases, metabolic disorders, inflammatory diseases, and infectious diseases.

However, there are several issues that must be addressed in future study. First, it is important to emphasize the study to characterize the phytochemical composition of carrots using established analytical methods or active markers, as well as the best extraction methods that optimize the yield. The raw carrots, which are essential parts of the studies, must be verified in terms of origin, cultivation condition, and plant identification. Such parameters are essential in such research to produce replicable outcomes in pharmacological or clinical trials, enabling appropriate comparability.Though, many studies have yet to specifically examine the biochemical components of carrots for bioactive qualities such as antioxidant, anti-inflammatory, and immunomodulatory activity. It is recommended that analysis of bioactive components be used to evaluate the immunomodulatory activity of carrots, because, in this literature review, one of the bioactive chemical components that have been specifically identified for their effect on modulating the immune system is β-carotene and falcarinol.

Second, many studies currently use carrot interventions in the form of juice or extract, whereas interventions using isolated bioactive compounds from carrots only include β-carotene and falcarinol. This is a concern since it is difficult to determine which bioactive compounds have been shown to be effective in immunomodulatory pathways when utilizing an intervention in the form of a mixture. Specific bioactive compound identification can be used to prevent misleading results. If this issue is not addressed, it will adversely affecting the studies' results. Then, in relation to experimental studies, it is crucial to extensively define the experimental procedures and compare he intervention with standard therapy in order to fully understand the function of active compounds from carrots in immune system modulation. Additionally, toxicological investigation is also necessary to ensure the continuity of clinical studies. Thus, further research was suggested to conduct Phase I to III clinical trials to determine the mechanisms, pharmacokinetics, safety and effectiveness of the immunomodulatory effects of carrots.

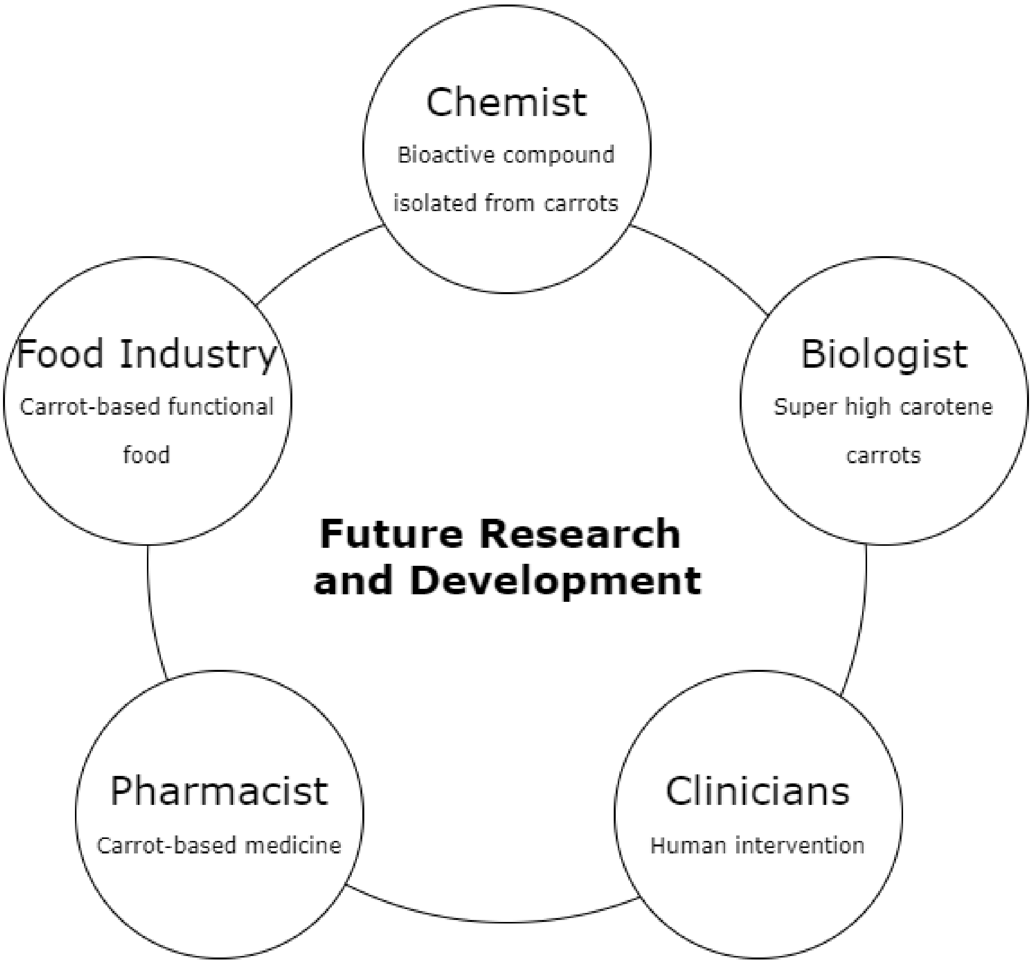



Figure 3. Carrot's immunomodulatory effect future research and development.

The ability of immune system to prevent diseases strongly influenced by the nutritional status of host. The discussion in this review suggested that the carrots can be used as a potent immunomodulator and when ingested could enhance the both cell-mediated and humoral immunity of host, either through their antioxidant or anti-inflammation properties. Carrots have the capacity to enhance the pharmaceutical, food, medical, and agricultural industries. Carrots are becoming increasingly popular as a result of increased public health awareness due to its high nutritional content and health advantages

In future, collaborations between researchers in various fields such as chemists, biologists, clinicians, and pharmacists as well as industrialist are needed for further exploration regarding the influence of carrots on the human immunity (Fig. 3). It has been explained that carrots contain bioactive compounds such as carotenoids, flavonoids, phenolic acids, polyacetylenes, and ascorbic acid, which have been proposed to have immunomodulatory effects; therefore, chemists may develop bioactive compounds isolated from carrots in the future. There has been a lot of development of genetically modified plant breeding to enhance the amount of phytonutrients and biomarkers for dietary health, for instance, red-fleshed apples are rich in anthocyanins (Espley et al., 2013; Sekido et al., 2010), therefore researchers in this area of expertise such as biologists may develop genetically modified carrots high in β-carotene in order to enriched the nutritional benefit of carrots.

Nutraceuticals can be used as alternative supplementation in disease management as well as to maintain a healthy lifestyle. Carrot-based nutraceutical products enriched with β-carotene and antioxidant properties have been developed in the form of carrot-mix juice, carrot jam, and carrot candies (Riaz et al., 2022). Other carrot-based product development is also encouraged in order to create a more diverse functional foods, therefore it can reach a broader consumer target. Furthermore, carrot-based supplements can also be developed by the pharmacists as single compounds or as phytocomplexes. Following pre-clinical and clinical research, carrot-based supplements or nutraceuticals can be used as human interventions as a complementary treatment in immune-related diseases.

Therefore, collaborations between researchers in various fields such as chemists, biologists, clinicians, and pharmacists as well as food industry are needed for further exploration regarding the influence of carrots on the human immunity (Fig. 3). Collaboration between researchers and industry can be a benefit in order to fasten the discoveries of this vegetable's benefits.

## 6. Conclusion

Carrot bioactive compounds such as β-carotene, phenolic acids, flavonoids, polyacetylenes, and ascorbic acid were found to have immunomodulatory activities via anti-inflammatory, antioxidant, and immune system pathways. On the anti-inflammatory pathway, the bioactive substances in carrots inhibition of pro-inflammatory responses and improvement of the anti-inflammatory cytokine levels, and promoted signaling pathways related to inflammation prevention. On the antioxidant pathway, carrots' bioactive substances carrots ameliorated oxidative stress by eliminating ROS and thus reduced oxidative stress parameters, increased antioxidant enzymes and oxidative stress prevention mechanism to achieve an improvement in antioxidant status. Immunomodulating effects of carrots also included the regulation of antibodies, leukocytes, immunoglobulins and histamine.

β-carotene is one of the most commonly encountered provitamin A and was abundant in carrots. β-carotene acts as an immunomodulator by regulating leukocyte formation and activity, enhancing immunoglobulin production, modulating inflammatory cytokine release, and decreasing pro-inflammatory mediators. One of the ways β-carotene controls the immune system is through redox balance alterations related to lipid peroxidation and antioxidant enzymes.

These immunomodulatory characteristics is one of the efforts to maintain the balance of immune response and oxidant-antioxidant status in the body. Thus, it could be suggested that carrots have the potential to maintain the optimal immunity. Many studies have yet to precisely study carrot's biochemical components for bioactive properties such as antioxidant, anti-inflammatory, and immunomodulatory activity. Collaborative works are suggested to further investigate bioactive components as well as underlying processes, specifically carrot immunomodulatory action and future accessability of carrot-based products.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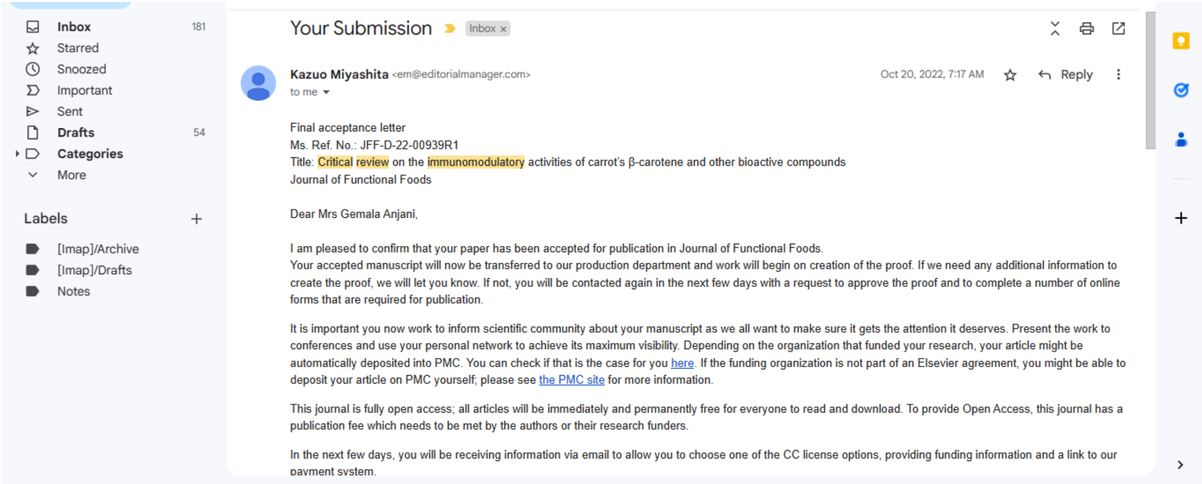


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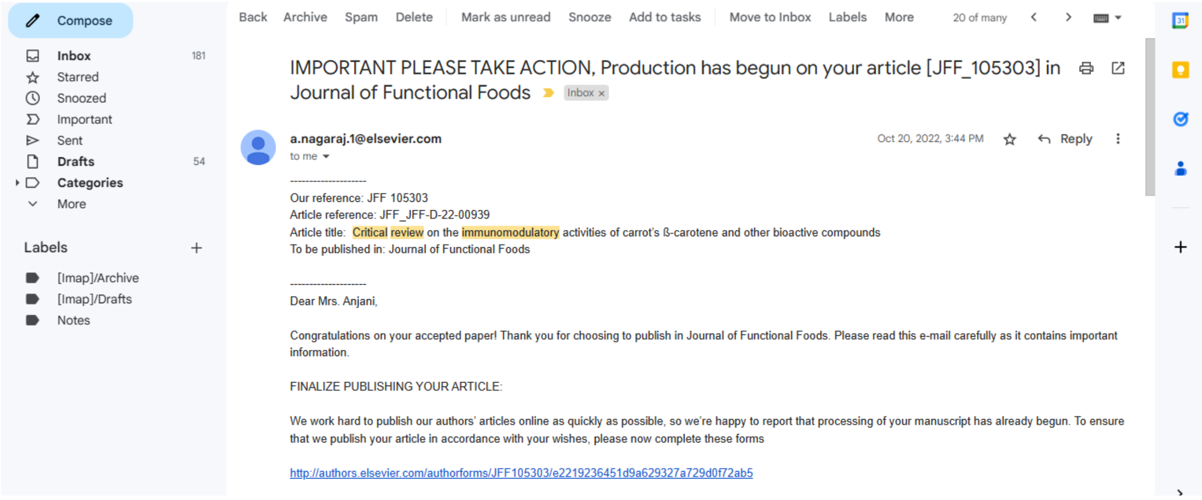

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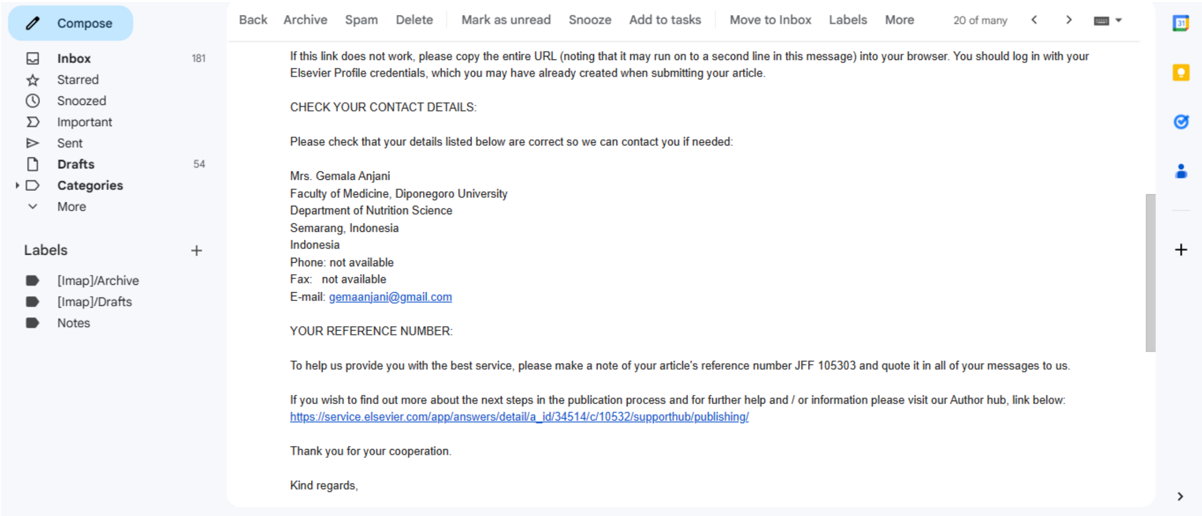

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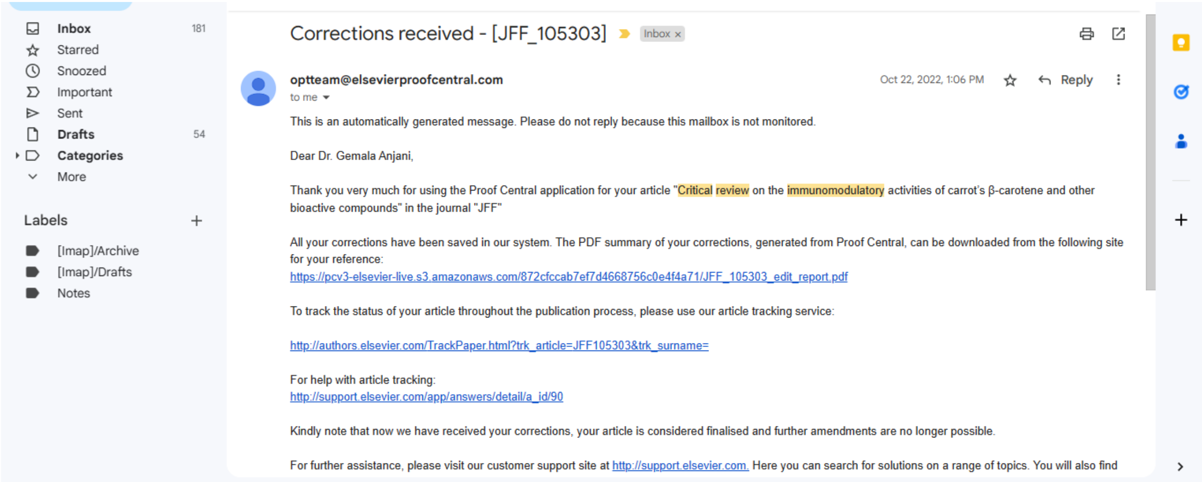

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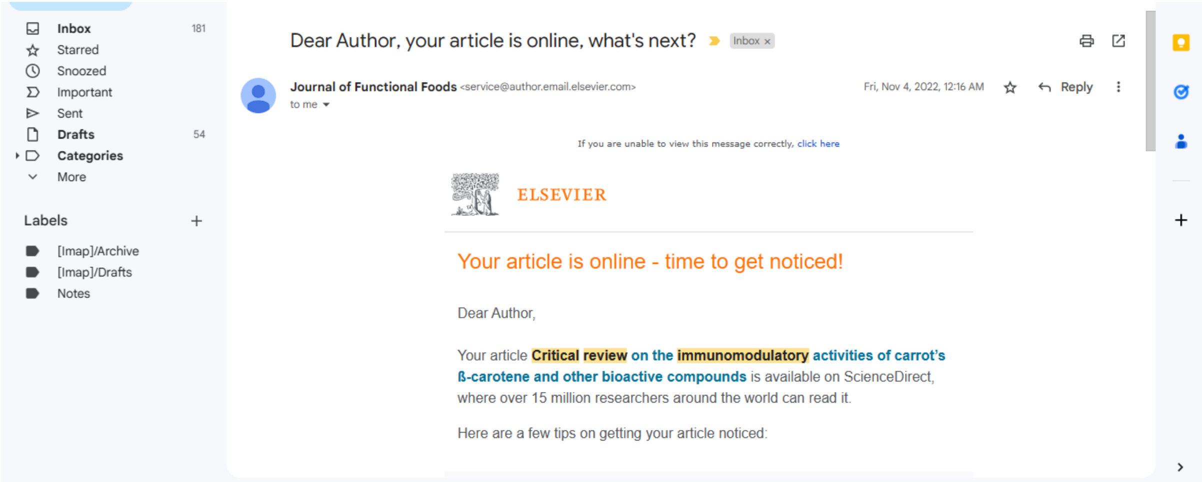

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# Critical review on the immunomodulatory activities of carrot's β-carotene and other bioactive compounds

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A R T I C L E I N F O

*Keywords:*
*Daucus carota* L.
Immunomodulator
Oxidative stress
Inflammation
Bioactive compound

A B S T R A C T

Carrots (*Daucus carota* L.) are vegetables proven to have nutraceutical effects and beneficial for health due to its natural bioactive substances. One of the potential of carrots to maintain optimum health status is by regulating immune response. This literature review summarized the proposed immunomodulatory mechanisms of the antioxidant properties of carrot's β-carotene and other bioactive compounds such as phenolic acid, flavonoid, polyacetylene and ascorbic acid via the anti-inflammatory, antioxidant and overall (innate and adaptive) immune response modulation. Overall, carrot's bioactive compounds regulated pro-inflammatory and anti-inflammatory cytokines, reduced oxidative stress by decreasing the reactive oxygen species accumulation and improving antioxidant capacity and the expression of genes in order to prevent more damaging oxidative destruction. Carrots also modulated the immune components by regulating leukocytes, antigens, immunoglobulins, and histamine levels. Thus, the immunomodulatory activity makes carrots as a functional food source that has the potential to prevent and treat various diseases.

## 1. Introduction

The immune system system is critical to the body's physiological and immunological function, therefore any disturbance in the immune system can lead to various diseases (Agita & Thaha, 2017; Coussens & Werb, 2002). The immune is a complex framework designed primarily of leukocytes and various immune components such as antibodies, proteins, and cytokines that act as the first defense mechanism against numerous harmful substances in the environment. This interplay of diverse immune components facilitates the establishment of an optimum immune response (Delves & Roitt, 2000). The immune system identifies and eliminates pathogens while inducing inflammation, cell or tissue damage, cell death, and wound healing in order to preserve redox balance in immune cells in order to prevent various disorders. If homeostasis is not maintained, immune-mediated diseases, metabolic disorders, and inflammatory diseases will develop, as well as susceptibily to infectious diseases such as corona virus disease of 2019 (COVID-19) (Adapa et al., 2011; Q. Li et al., 2022; Nardy et al., 2015; Paragh et al., 2014).

Nutrition is one of the factors that influences the immune system. For

*Abbreviations:* ABTS, 2,2′-azinobis-(3-ethylbenzthiazolin-6-sulfonic acid); ALT, alanine transaminase; APAP, acetaminophen; ARDS, acute respiratory distress syndrome; ASCVD, atherosclerotic factors of cardiovascular disease; AST, aspartate transaminase; Bcmo1$^{-/-}$, β-carotene 15,15′-monooxygenase 1 knockout; CD4, clusters of differentiation; con-A, concavalin-A; COVID-19, corona virus disease of 2019; COX2, cyclooxygenase-2; CUPRAC, cupric reducing antioxidant capacity; FFA, free fatty acid; FRAP, ferric reducing antioxidant power; GPx, glutathione peroxidase; HO-1, heme oxygenase-I; hsCRP, high-sensitivity C-reactive protein; IBD, inflammatory bowel disease; IFN-γ, interferon γ; IgA, immunoglobulin A; IgE, immunoglobulin E; IL, interleukin; JAK-STAT, janus kinase-signal transducer and activator of transcription; JNK, jun *N*-terminal kinase; LPS, lipopolisaccharide; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; NFκB, nuclear factor kappa-B; NK-cell, natural killer-cell; NLRP3, the nucleotide-binding domain (NOD)-like receptor protein 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PGE2, prostaglandin E2; RA, rheumatoid arthritis; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; Th, T helper; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; Treg, regulatory T cells; USDA, United States Department of Agriculture.

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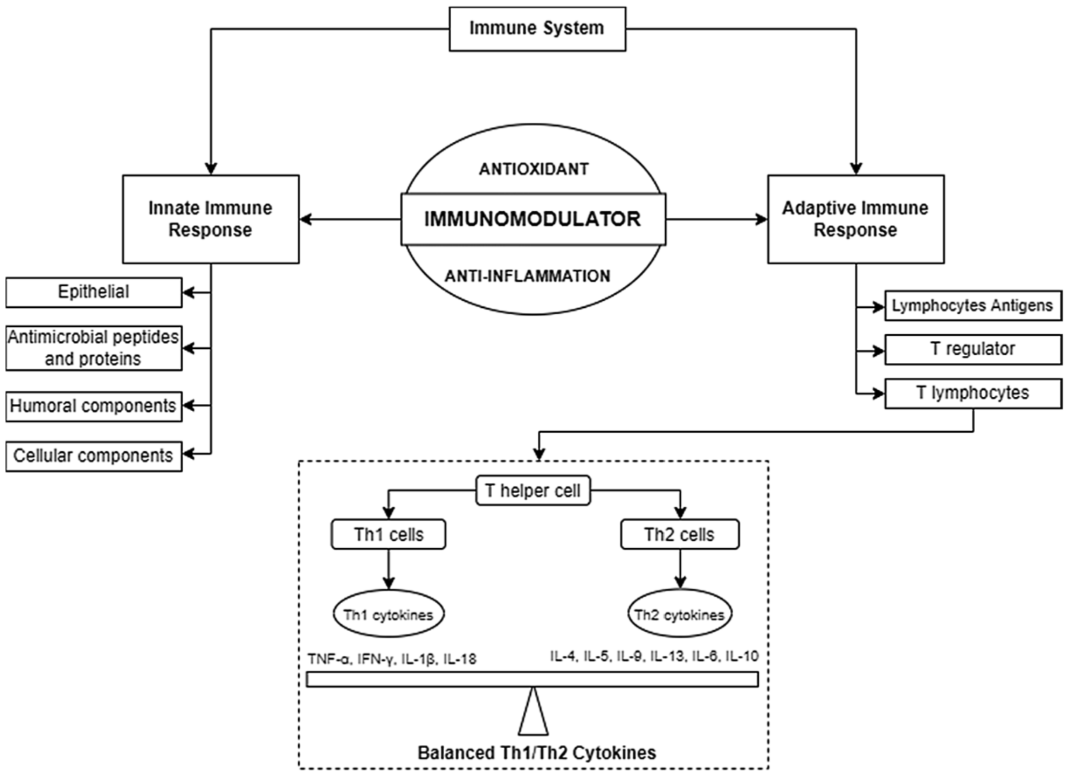


**Fig. 1.** Immunomodulator Mechanism via Antioxidant and anti-Inflammation Properties. Th1, T helper type 1; Th2, T helper type 2; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; IL, interleukin.

instance, nutritional deficit may result in decreased immune responses, and supplementation of those specific components would often restore the compromised immune responses (Venter et al., 2020). Optimal nutrition intake affects the immune response through regulating various genes expression and signaling molecules (Farhan Aslam et al., 2017). Immunomodulators are components that regulate the body's immune system (Venkatalakshmi et al., 2016). Immunomodulators are not only available in endogenous form, but also from exogenous sources whose mechanism of action is often based on antioxidant properties. Studies have been able to prove that some natural antioxidants from plants can act as natural immunomodulators. Immunomodulators from antioxidant source maintain health status through regulation of the oxidant-antioxidant balance and immune response. Antioxidants operate either directly or indirectly, by eliminating reactive oxygen–nitrogen species or enhancing the body's antioxidant balance, so that immune and inflammatory responses may be regulated (Ortuño-Sahagún et al., 2017).

Currently, many bioactive compounds from plants have been investigated for their potential benefits as immunomodulators (Venkatalakshmi et al., 2016). Turmeric, Echinacea, green tea, and chili pepper are examples of plant sources with immunomodulatory effects (Catanzaro et al., 2018; Grüter et al., 2020; Hasan et al., 2021; Rahayu et al., 2018). However, intake from some of these sources are still limited. Carrots *(Daucus carota* L.) are beneficial vegetables in the world due to its massive production and its usage as food for public daily intake, both in fresh and processed form. This vegetable has nutraceutical effects and is beneficial for health due to its high natural bioactive substances (Ahmad et al., 2019).

Carrots' main carotenoid is β-carotene, a well-known and extensively researched carotenoid. Carotenoids are phytonutrients that give fruits and vegetables their unique yellow, orange, and red hues. β-carotene provides a variety of health benefits in addition to providing color in food. It has a high antioxidant capacity and provides a number of health advantages, including decreasing the risk of certain illnesses and cancers, strengthening the immune system, and protecting against age-related eye degeneration (Gul et al., 2015).

A recent review has shown that carrots act as antioxidants, antidiabetic, antimicrobial, nephroprotective, hepatoprotective, cardioprotective, anti-inflammatory and wound healing properties (Al-Snafi, 2017). Moreover, carrots can also improve the immune system and eye health (da Silva Dias, 2014; Mahammad Shakheel et al., 2017). The previous review examined the protective effect of β-carotene against gastric cancer based on epidemiological surveys (Chen et al., 2021). In addition, β-carotene also plays a role in stimulating lipid catabolism, which metabolizes lipids, which is one of the atherosclerotic factors of cardiovascular disease (ASCVD) (Miller et al., 2020).

Although prior review have addressed the health benefits of carrot bioactive compounds (da Silva Dias, 2014), especially β-carotene, the specific immunomodulatory activities have not been well investigated as the mechanism is known to be exceedingly complicated and remain unclear. An experimental research discovered that administration of carrot juice improved antioxidant capacity and decreased malondialdehyde after 3 months consumption of carrot juice (Potter et al., 2011). A randomized cross-over study also noted an improvement in interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α) in healthy men after consumption of carrot juice or tomato juice in healthy men after conducting 2-weeks low carotenoid periods (Watzl et al., 2003). Therefore, the purpose of this literature review is to explore into the potential immunomodulatory mechanism of carrots' β-carotene and its other bioactive compound.

## 2. Immunomodulator

Immunomodulator is defined as substance that modulate the immunological response, either decreasing the immune response as a type of therapy for autoimmune diseases or enhancing the immune response to immuno-compromised conditions (Ilyas et al., 2016). Immune system is defined as the body's natural defense system against disease and disorders (Sharma et al., 2017). The immune system is divided into innate and adaptive immune systems, both of which determine a person's ability to fight harmful agents. Innate immunity is known as the first defense against pathogens and consists of epithelial protection, antimicrobial proteins and peptides, humoral and cellular components. Then, the adaptive immune system was activated by the innate immune systems, which contributed in the foreign antigen recognitions (Tyagi, 2016). The adaptive immune responses consist of B lymphocytes with antigens, T lymphocytes and regulatory T cells (Treg) (Sharpe & Mount, 2015).

The main source of cytokines in the body is the T lymphocytes, in which these cells have specific antigen receptors that enable pathogen recognitions. T lymphocytes expressing the clusters of differentiation 4 (CD4) are known as T helper (Th) cells. This subset is further subdivided into Th1 and Th2 cells, which produce Th1 and Th2 cytokines, respectively. Th1 cytokines tend to act as pro-inflammatory agents for intracellular pathogens elimination. Th1 cytokines include TNF-α, interferon γ (IFN-γ), interleukin 1β (IL-1β), IL-2 and interleukin 18 (IL-18). Th2 cytokines, on the other hand, are known to be more complex. Th2 cytokines include the immunoglobulin response-related cytokines such as interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 9 (IL-9), and interleukin (IL-13), as well as pro-inflammatory interleukin 6 (IL-6) and anti-inflammatory interleukin (IL-10). As a result, a balance of Th1 and Th2 responses is required in order to combat pathogens effectively while avoiding uncontrollable inflammation (Berger, 2000).

Inflammation is known as a normal physiological response of the body's immune system to counter harmful stimuli such as infections, damaged cells and toxic compounds. Inflammatory responses, whether acute or chronic, can cause tissue damage or disorders in the heart, pancreas, liver, kidneys, lungs, brain, gastrointestinal tract, and reproductive system. Infectious and non-infectious agents, as well as cell damage, usually activate inflammatory signaling pathways such as nuclear factor kappa-B (NFκB), mitogen-activated protein kinases (MAPK), and janus kinase-signal transducer and activator of transcription (JAK-STAT) (Chen et al., 2018). Excessive inflammation exacerbates functional disorders and tissue injuries (Bartold & Dyke, 2017). For example, the hyper-inflammation that occurs in COVID-19 causes a "cytokine storm" leading to acute respiratory distress syndrome (ARDS), pneumonia, organ failures, fibrosis, or even death (Channappanavar & Perlman, 2017; Shi et al., 2020).

During the homeostatic state, several endogenous and external factors contribute to immunosuppression and immuno-stimulation (Jantan et al., 2015), thus affecting the innate and adaptive immune response (Fig. 1). Immune response modulation occurred to regulate the body's immune response in therapeutic and preventive attempts against causative agents (Rasheed et al., 2016; Razali et al., 2016). The use of immunomodulators is presently-one of the most pressing issues in the treatment of numerous diseases (Sharma et al., 2015).

Application of plant-derived bioactive compounds has become one of the primary areas of exploration for the natural immunomodulators (Shukla et al., 2014). The use of natural immunomodulators is currently increasingly being accepted in the world because of their wide range in preventing and treating disease via changes in immune response or oxidant-antioxidant status (Ajith et al., 2017).

The antioxidant defense system involves free radical reduction, antioxidant enzyme activation and maintenance, enhancement of other antioxidant mechanisms, and specific immunomodulatory effects (Ajith et al., 2017). Plants that serve as natural immunomodulators have the capacity to boost immunity by activating innate immune responses such as activating immune cellular components, modifying cytokine profiles, decreasing infection and inflammation. The immunomodulatory properties of these plants cannot be separated from their bioactive compounds (Jantan et al., 2015).

## 3. Nutrition and bioactive contents of carrots

*Daucus carota* L., or commonly known as carrot, is a vegetable belonging to the *Apiaceae* family (Bussmann et al., 2020). Based on FAOSTAT 2021 data from the Food and Agriculture Organization (FAO), in 2019, nearly 44.8 million tons of carrots and radishes were widely produced for daily consumption (FAOSTAT, 2021). Carrots consist of stems and roots in which the roots consist of the periderm, outer cortex (phloem) and nucleus (xylem). The part of the carrot that is commonly consumed is the root. High quality carrots have a greater proportion of phloem than xylem (Char, 2018). The taxonomy of carrots from the Integrated Taxonomic Information System (2022) database are as follows:

Kingdom: *Plantae*.
Sub Kingdom: *Viridiplantae*.
Division: *Tracheophyta*.
Sub Division: *Spermatophytina*.
Class: *Magnoliopsida*.
Order: *Apiales*.
Family: *Apiaceae*.
Genus: *Daucus* L.
Species: *Daucus carota* L.

Orange carrots are the dominant type of carrots and are mostly used in various cuisines both fresh or cooked. The rate of carrot consumption

**Table 1**
Nutrition and Bioactive Contents in Carrots (per 100 g FW).

| Component | Amounts | Unit | Reference | RDA (age 10–12 y.o) |
|---|---|---|---|---|
| Energy | 41 | kcal | USDA, 2015 | 2.05 % |
| Proximate | | | | |
| Moisture | 88,3 | g | USDA, 2015 | 4,77 % |
| Carbohydrate | 9,58 | g | USDA, 2015 | 3,19 % |
| Protein | 0,93 | g | USDA, 2015 | 1.86 % |
| Fat | 0,24 | g | USDA, 2015 | 0,37 % |
| Fibre | 2,80 | g | USDA, 2015 | 10 % |
| Ash | 0,97 | g | USDA, 2015 | 4,77 % |
| Iron | 0,3 | mg | USDA, 2015 | 3.75 % |
| Magnesium | 12 | mg | USDA, 2015 | 7.5 % |
| Phosphorus | 35 | mg | USDA, 2015 | 2.8 % |
| Potassium | 320 | mg | USDA, 2015 | 8.21 % |
| Sodium | 69 | mg | USDA, 2015 | 3.63 % |
| Calcium | 33 | mg | USDA, 2015 | 2.75 % |
| Zinc | 0,24 | mg | USDA, 2015 | 3 % |
| Manganese | 0,14 | mg | USDA, 2015 | 26,6% |
| Vitamin B2 | 0,06 | mg | USDA, 2015 | 4.61 % |
| Vitamin B3 | 0,98 | mg | USDA, 2015 | 8.17 % |
| Folate | 19 | μg | USDA, 2015 | 4.75 % |
| Vitamin C | 5,90 | mg | USDA, 2015 | 11.8 % |
| Total Flavonoid | 4,50 | mg | Bahorun et al., 2004 | – |
| Quercetin | 1,50 | mg | Bahorun et al., 2004 | – |
| Luteolin | 0,80 | mg | Bahorun et al., 2004 | – |
| Kaempferol | 0,60 | mg | Bahorun et al., 2004 | – |
| Total Phenolic | 89,30 | mg | Hellström et al., 2020 | – |
| Caffeic acid | 41,10 | mg | Hellström et al., 2020 | – |
| Ferulic acid | 7,10 | mg | Hellström et al., 2020 | – |
| p-coumaric acid | 73,10 | μg | Rozan, 2017 | – |
| Carotenoids | 12,71 | mg βCE | Rozan, 2017 | – |
| α-carotene | 3,38 | mg | Rozan, 2017 | – |
| β-carotene | 8,21 | mg | Rozan, 2017 | – |
| *Falcarinol* | 359–1900 | μg | Rawson et al., 2010 | – |
| *Falcarnidiol* | 154–18000 | μg | Acworth et al., 2011 | – |
| *Falcarni-acetate* | 77–140 | μg | Acworth et al., 2011 | – |

Abbreviation: USDA, United States Department of Agriculture.

**Table 2**
The Roles of Carrot and its bioactive compound as immunomodulatory.

| Subjects | Study Design | Preparation | Dose | Route | Duration | Immunomodulatory Activity | Modulation | Parameters/Mediator Affected | Ref |
|---|---|---|---|---|---|---|---|---|---|
| BALB/c mice | *In vivo* | Organic and conventional carrots | 70 g/kg of feed | Oral | 30 days | immunostimulant in intestinal and peripheral immunity | ↑ | Lymphocyte population, including Treg | Roselli et al., (2012) |
| APAP-induced oxidative stress BALB/c mice | *In vivo* | Carrot deuterium-depleted aqueous extract | 500 mg/kg | Oral | 7 days | Oxidative stress indicators | ↓ | ALT, AST and 8-OHdG | Saba et al., (2019) |
| | | | | | | Antioxidant enzyme | ↑ | SOD | |
| Cadmium-induced oxidative cytotoxic damage in rats | *In vivo* | Carrot juice | *ad libitum* | Oral | 5 days | Improve endogenous antioxidant | ↑ | Catalase, SOD, GPx | Embugushiki et al., (2013) |
| High fructose diet-induced inflammation in weaning wistar rats | *In vivo* | Carrot juice | 0.6 mL | Oral | 8 weeks | Pro-inflammatory mediator | ↓ | MCP1 and hsCRP | Mahesh et al., (2017) |
| LPS-induced CB57BL/6 mice | *In vivo* | Carrot's falcarinol | 5 mg/kgBW | Oral | 7 days | Immune homeostasis's regulator | ↑ | Heme oxygenase-1 8.42 times in mRNA levels and 10.7 times in protein levels | Stefanson & Bakovic, (2020) |
| | | | | | | Cytokine release | ↑ | Plasma IL-4, IL-9, IL-10, IL-13, illustrating the characteristics in the improvement of type 1 inflammation | |
| LPS-induced CB57BL/6 mice | *In vivo* | Carrot's falcarinol | 5 mg/kgBW | Oral | 7 days | Pro-inflammatory cytokines | ↓ | IL-6, TNF-α/TNF-αr, and IFNγ gene expression | Stefanson & Bakovic, (2018) |
| Albino wistar rats | *In vivo* | Carotenoid extract from carrots | 559 mg/kg | Oral | 21 days | White blood cells | ↑ | lymphocytes, eosinophils, monocyte counts | Ekam et al., (2006) |

↓, decrease; ↑, increase;
Abbreviations: APAP, Acetaminophen; LPS, lipopolisaccharide; Treg, T regulator; SOD, superoxide dismutase; GPx, glutathione peroxidase; MCP-1, monocyte chemoattractant protein-1; hsCRP, high-sensitivity C-reactive protein; ALT, alanine transaminase; AST, aspartate transaminase; IL, interleukin; TNF-α, tumor necrosis factor-alpha

increased due to an increase in public awareness of carrots as functional food that is useful in supporting healthy lifestyle (Ergun, 2018). The antioxidant activity of orange carrots based on the Ferric Reducing Antioxidant Power (FRAP), 2,2′-Azinobis-(3-Ethylbenzthiazolin-6-Sulfonic Acid) (ABTS) and Cupric Reducing Antioxidant Capacity (CUPRAC) were 1.22 mol TE/g, 1.22 mol TE/g and 3.07 mol TE/g fresh weight, respectively (Singh et al., 2018). The following Table 1 presents data on the nutritional and bioactive content of carrots.

## 4. Potential of carrots as immunomodulator

Carrots and their phytochemical compounds have been shown to have potential as a natural immunomodulator through both antioxidant and anti-inflammation properties, or by their modulation to other immune components (Table 2). For example, Roselli et al. (2012) indicated that organic carrot consumption at a rate of 70 mg/kg of feed for 30 days stimulated intestinal and peripheral immunity, with an increase in lymphocytes, including Treg. Saba et al. (2019) showed an improvement in superoxide dismutase (SOD) after administration of carrot extract at the dose of 500 mg/kg for 7 days in oxidative stress rats model. SOD controls extracellular reactive oxygen species (ROS), which are known to cause collateral tissue damage even though they are essential for the immune system's defense against pathogens (Break et al., 2012). In a cytotoxic oxidative tissue damage model, Embugushiki et al. (2013) also observed an improvement in the activity of antioxidant enzymes after 5 days of carrot juice intervention (as drinking water). As previously stated, increasing the body's antioxidant status by administrating natural antioxidant counteracts the impacts of inflammation and further tissue injury through improvement of oxidative stress (Arulselvan et al., 2016).

The body is constantly in a condition of equilibrium between the formation and elimination of free radicals. The catalase, glutathione reductase, and SOD antioxidant enzymes, as well as glutathione, urate, coenzyme Q, or exogenous stimuli such bioactive substances like β-carotene, are all parts of the body's natural defensive system against free radicals. Because of the neutrophil-produced free radicals, the immune system's defense against infections serves as one of the sources of ROS generation. Micronutrient deficiency was known to cause a deterioration in immune function, both innate and adaptive, thereby rendering the body susceptible to pathogen attack as a consequence of immune imbalance. Thus, it was critical to consume bioactive compounds that serve as antioxidants in order to maintain a balanced immune response (Brambilla et al., 2008).

Carrots contain a variety of bioactive compounds, including flavonoids, phenolic acids, carotenoids, polyacetylene, and ascorbic acid. Those bioactive compound was shown to have immunomodulatory properties due to their antioxidant, anti-inflammatory, and regulatory properties of innate and adaptive immune response components. These modulatory activities included the suppression and stimulation of inflammatory cytokines, antioxidative activity through ROS scavenging

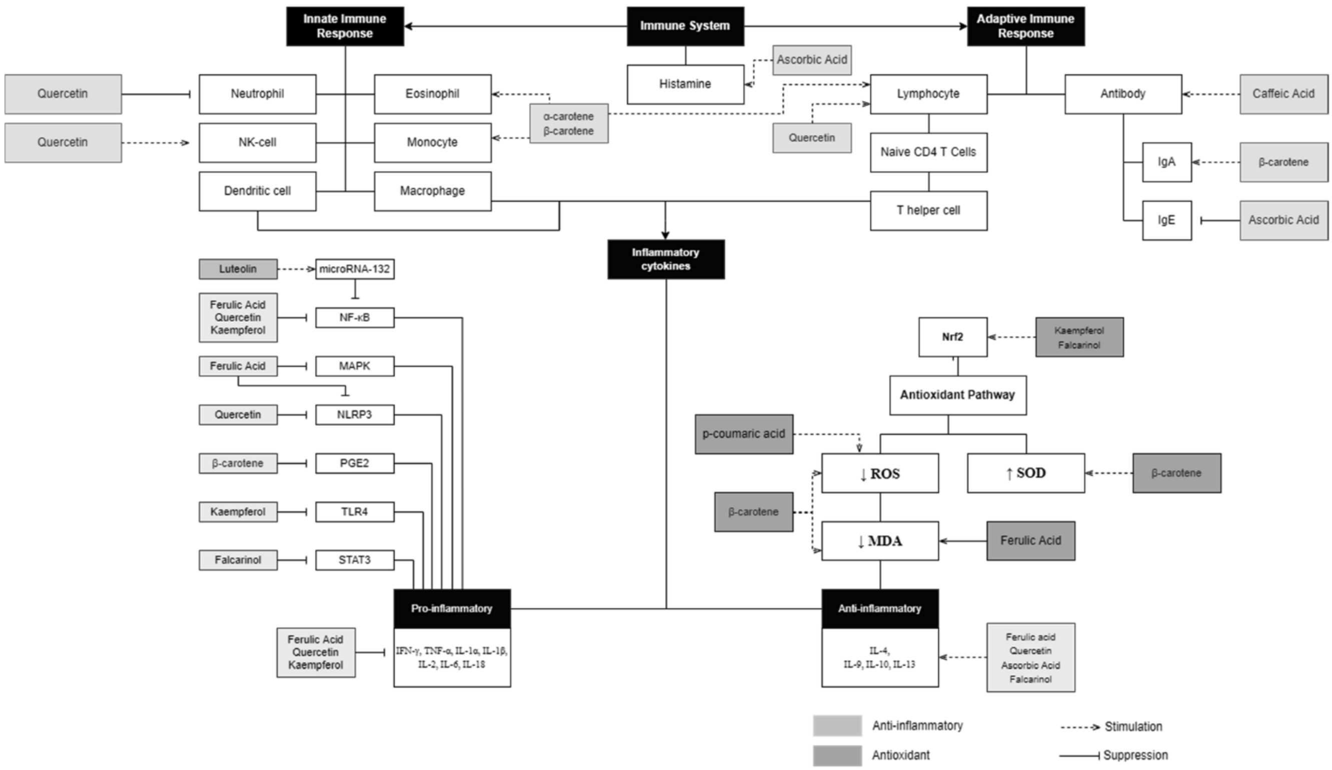


**Fig. 2.** Summary of Potential Immunomodulatory Mechanisms of Bioactive Compounds in Carrots. NK-cell, natural killer-cell; CD4, cluster of differentiation 4; IgA, Immunoglobulin A; IgE, Immunoglobulin E; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; NLRP3, the nucleotide-binding domain (NOD)-like receptor protein 3; PGE2, prostaglandin E2; TLR4, toll-like receptor 4; STAT3, signal transducer and activator of transcription 3; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; IL, interleukin.

activity and improvement in endogenous antioxidant defense, as well as modulating pro-inflammatory and anti-inflammatory signaling pathways (Fig. 2).

Carotenoids are isoprenoids present in a variety of plants, including carrots. Carotenoids are acyclic molecules with five to six C rings at one or both ends (Sharma et al., 2012). Carotenoids' color variation is caused by conjugated double bonds in polyene chains that function as chromophore (Rodriguez-Concepcion & Stange, 2013; Ruiz-Sola & Rodríguez-Concepción, 2012). The main carotenoids present in orange carrots are α-carotene and β-carotene (Søltoft et al., 2011).

β-carotene is a secondary metabolite produced by plants that belongs to the non-oxidized carotenoids group. β-carotene possesses a long chain of conjugated double bonds due to its role as a polyene compound of the derived acyclic structure (Fratianni et al., 2010; Meléndez-Martínez et al., 2010). Carotenoids, which have the same structure as retinol molecules, exhibit vitamin A activity, with β-carotene having the highest bioactivity as a vitamin A precursor. It is the most potent vitamin A precursor and occurs naturally as a combination of several isomers (cis and trans) of the β-carotene molecule (Toti et al., 2018). *In vivo* model indicated that long-term consumption of β-carotene reduced the production of malondialdehyde (MDA), the end product of lipid peroxidation (Hosseini et al., 2010).

MDA is an oxidative stress biomarker that contributes in maintaining balance of physiological functions, including innate and adaptive immune responses, thus affecting pathological conditions such as neurodegenerative diseases, metabolic diseases, cancers and also infectious diseases (Papac-Milicevic et al., 2016). For instance, in some autoimmune disorders, such as systemic lupus erythematosus (SLE), MDA levels are elevated due to metabolic dysregulation and increased ROS. Suppressing excess MDA in interventions is therefore advantageous (Hardt et al., 2018).

### 4.1. *Immunomodulatory effect of β-carotene*

Katsuura et al. (2009) showed that β-carotene administration in a time and dose-dependent manner was positively correlated with lipid peroxidation and glutathione synthesis, as well as negatively correlated with the transcription of cytokines such as IL-1β, IL-6, and IL-12, in lipopoliscaccharide (LPS) and INF-gamma-induced RAW264 cells. This indicated that β-carotene triggers changes in intracellular redox status thereby regulating the immune function of macrophages.

Monocyte chemoattractant protein-1 (MCP-1) is a CC-chemokine that plays an important role in the inflammatory process by attracting or increasing the expression of inflammatory factors/cells. MCP-1 is involved in the pathogenesis of a variety of diseases, both directly and indirectly, including COVID-19, cancer, neuroinflammatory diseases, rheumatoid arthritis, and cardiovascular disease (Deshmane et al., 2009). In high-fructose diet-induced weaning rats, Mahesh et al. (2017) demonstrated that 0.3 mL of β-carotene from carrot juice reduced the level of free fatty acid (FFA), MCP-1 and high-sensitivity C-reactive protein (hsCRP) by 50 %, 32 % and 40 % respectively. Ekam et al., (2006) analyzed the immunomodulatory effect of carotenoid extracts (α-carotene and β-carotene) of carrots at a dose of 559 mg/kg for 21 days, increased levels of lymphocytes, eosinophils, monocytes and platelets in male Wistar rats was observed.

In their investigation on weanling mice, Nishida et al. (2014) discovered that β-carotene supplementation at a dose of 50 mg/kg feed for 14 weeks elevated the synthesis of immunoglobulin A (IgA) in the jejunum or ileum. Retinoic acid-mediated immune response was responsible for this outcome. Considering neonate and children are susceptible to diarrhea and gastrointestinal infections, that study also found an improvement in the immune response in the gastrointestinal tract (Nishida et al., 2014). Nishiyama et al. (2011) investigated the effect of β-carotene supplementation in pregnant mice during pregnancy and lactation on IgA parameters from mammary glands, guts, and transfer of IgA from milk to neonate mice. Administration of 50 mg/kg of β-carotene supplements from 6.5 days postcoitus to 14 days postpartum showed an increased presence of IgA in the mammary glands and ileum during lactation, thereby triggering increased transfer of maternal milk IgA to neonate mice. IgA is the most abundant type of antibody in the body, and it protects mucous glands from microbial invasion while also maintaining immune homeostasis in the gastrointestinal, respiratory, and vaginal tracts. The protective immune response against intestinal viral enteropathogens was dependent on the presence of this immunoglobulin, which demonstrated the importance of IgA (Blutt et al., 2012).

The JAK-STAT pathway is critical in combating the immune system's challenges, extending from infection prevention to cancer protection. This function, however, must be maintained. Excessive and prolonged JAK-STAT signaling occurs in practically all types of autoimmune disorders (Villarino et al., 2015), as well as arthritis, Alzheimer disease, and osteosarcoma (Chiba et al., 2009; Saravanan et al., 2014; Yan et al., 2015). Signal transducer and activator of transcription 3 (STAT3), specifically, also contributes in the development of inflammatory disease such as periodontitis and cancers (De Souza et al., 2011; Geiger et al., 2016). One of the primary functions of the jun *N*-terminal kinase (JNK)/p38 MAPK is to regulate the immune response, particularly in activating stress. Therefore, pharmacological interventions capable of inhibiting these pathways have been shown to be effective in alleviating inflammation in the those diseases (Jeffrey et al., 2007; Kumar et al., 2003; Manning & Davis, 2003). Yang et al. (2021) showed that administration of β-carotene for 7 days remarkably reduced production of nitric oxide (NO), prostaglandin E2 (PGE2), TNF-α, and IL-1β in LPS-induced intestinal inflammation. Moreover, there was suppression of mRNA expression of IL-1β and TNF-α was observed after intervention. The postulated mechanisms for these findings included autophagy regulation as well as JAK2/STAT3 and JNK/p38 MAPK inflammatory pathways.

According to a prior review, β-carotene inhibits ROS-mediated inflammatory signaling, including the MAPK pathway and redox-sensitive transcription factors, as well as the production of inflammatory mediators including IL-8, nitric oxide synthase (NOS), and cyclooxygenase-2 (COX2) (Kang & Kim, 2017). The anti-inflammation mechanism of β-carotene was related to the reduction of the NFκB inflammatory pathway and suppression of ROS production (Di Tomo et al., 2012). A variety of inflammatory disorders, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis, atherosclerosis, SLE, type I diabetes, chronic obstructive pulmonary disease, and "cytokine storm" in COVID-19, have been linked to NFκB activation (Hariharan et al., 2021; Pai & Thomas, 2008). Since uncontrolled NFκB activation is linked to these multiple inflammatory conditions, targeting NFκB signaling is a viable approach for anti-inflammatory therapy (Liu, Zhang et al., 2017, Liu, Shen et al., 2017). Zhou et al. (2018) discovered that β-carotene blocked the NFκB activation pathway and diminished the production of pro-inflammatory cytokines. Furthermore, this study revealed that β-carotene treatment markedly reduced oxidative stress by lowering ROS, MDA, and NO while increasing SOD. van Helden et al. (2013) showed a depletion in mRNA expression of pro-inflammatory genes associated with the NFκB pathway involved in the production and regulation of IFN in lungs, liver and adipose tissue in β-carotene 15,15′-monooxygenase 1 knockout (Bcmo1$^{-/-}$) mice after 14 days of β-carotene supplement intervention.

### 4.2. *Other bioactive compound in carrots as immunomodulator*

#### 4.2.1. *Phenolic acid and flavonoid*

The most abundant phenolic acid in carrots is chlorogenic acid, such as caffeic, ferulic and p-coumaric acids (Arscott & Tanumihardjo, 2010). Caffeic acid influenced antibody production and inflammatory signaling, improving oxidative state in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected individuals (Adem et al., 2021). Ferulic acid pre-treatment (50 mg/kg) for 30 days reduced LPS-induced inflammation by upregulating IL-1, IL-6, TNF-α, and IL-10 production. Acute ARDS was improved by ferulic acid's antioxidative and anti-inflammatory effects via inhibition of the MAPK inflammatory pathway, which subsequently resulted in decreased MDA and myeloperoxidase, as well as an increase in antioxidant status (Zhang et al., 2018). Other study had shown that ferulic acid intervention for 4 weeks regulated NFκB pathway at the dose of 40 mg/kg and the nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome at the doses of 40 and 80 mg/kg, characterized by decreased levels of TNF-α, IL-1β, and IL-6 mRNA expression in stressed-induced mice (Liu, Zhang et al., 2017, Liu, Shen et al., 2017).

Like NFkB, the NLRP3 inflammasome promotes inflammation. In several inflammatory conditions like Alzheimer's, atherosclerosis, atrial fibrillation, osteoarthritis, cancer, and autoimmune illnesses like SLE and IBD, NLRP3 modulate the inflammation response in innate immune system (Wang et al., 2020). On the contrary, NLRP3′s role in inflammation makes it essential for the elimination of viruses (Zhao & Zhao, 2020). Thus, modulating these pathways is vital for therapeutic treatment. P-coumaric acid had been shown to ameliorate LPS-induced oxidative damage through ROS scavenging activity and oxidative stress improvement in inflammatory state of the lungs (Kheiry et al., 2020).

The main flavonoids detected in orange carrots were quercetin, luteolin and kaempferol (Bahorun et al., 2004). Quercetin inhibited NFκB and IL-6 signaling, which exhibited an anti-inflammatory impact. The administration of quercetin remarkably reduced LPS-induced lung inflammation, as seen by lower levels of neutrophils, lymphocytes, and pro-inflammatory cytokines in the lungs (Huang et al., 2015). Quercetin also inhibited the activation of the NLRP3 inflammasome, IL-1α, IL-6, and IL-18 secretion (Jiang et al., 2016). Luteolin at a dose of 50 mg/kg reduced TNF-α, IL-1β and IL-6 production (Lodhi et al., 2020). In LPS-induced bronchopneumonia model, luteolin reduces inflammatory injury by regulating the expression of microRNA-132, thereby inhibiting NFκB pathway (Liu & Meng, 2018). microRNA-132 is RNA molecule the involved in the inflammation suppression during wound healing (Li et al., 2015). Kaempferol acted as an anti-inflammatory agent by suppressing the binding of NFκB from DNA decreasing the secretion of pro-inflammatory cytokines, inhibiting toll-like receptor 4 (TLR4) which acted as a trigger in pro-inflammatory response, and increasing expression of nuclear factor target gene mRNA and nuclear factor E2-related factor 2 (Nrf2) which was involved in oxidative damage prevention (Nam et al., 2017; Saw et al., 2014; Tang et al., 2015; R. Zhang et al., 2017). It may be inferred that the majority of these flavonoids and phenolic acids' immunological actions are connected to their anti-inflammatory properties and facilitate the protection of oxidative damage. This is important since many inflammatory and infectious diseases depend on the inflammatory process, as demonstrated by its influence on lung disorders like as ARDS, bronchopneumonia, and lung inflammation.

#### 4.2.2. *Polyacetylene*

Polyacetylene is a non-volatile phytochemical group consisting of at least two C—C triple bonds. Carrots contain polyacetylene such as falcarinol, falcarindiol, and falcarindiol 3-acetate (Christensen, 2012; Dawid et al., 2015). Recent review showed that polyacetylene has the potential in improving health status due to its antitumor, antifungal, anti-inflammatory, antibacterial and serotogenic properties (Dawid et al., 2015).

The transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) defend against intestinal inflammation and oxidative damage. Falcarinol was shown to be a dietary immunosuppressant in individuals with gastrointestinal inflammation, such as IBD, celiac disease, colitis, and enteritis (Stefanson & Bakovic 2020). Stefanson & Bakovic (2020) proved that falcarinol extract supplementation of 5 mg/kg given twice daily for a week enhanced the heme oxygenase-I (HO-1) expression, which is the target enzyme of Nrf2. This research also observed an increase in IL-4, IL-9, IL-10, and IL-13, indicating a decrease in inflammation after falcarinol ethanolic extracts administration in LPS-induced oxidative stress mice. Stefanson & Bakovic (2018) also demonstrated that pre-treatment of falcarinol extract at a dose of 5 mg/kg twice a day for 7 days prevented pro-inflammatory genes elevation proving its protective effect against systemic and intestinal inflammation in LPS-induced CB57BL/6 mice. That study discovered that LPS induction increased the expression of pro-inflammatory genes such as *IL-6* up to 103.6-fold, *Tnfα* up to 48.8-fold, *Tnfα* receptor (*Tnfαr*) up to 5.1-fold, *Ifnγ* up to 22.3-fold, and STAT3 3.6 times. In the presence of pre-treatment of the falcarinol ethanol extract, the expression level of pro-inflammatory genes (*IL-6*, *Tnfα/Tnfar* and *Ifnγ*) was equivalent to that of the negative control (not LPS induced), and the expression of STAT3 increased 2-fold. Gastrointestinal inflammation is an important issue because disruption of the gastrointestinal barrier is an indication of early deviations from body's homeostasis state, which lead to the development of more serious and various diseases such as autoimmune, food allergy, obesity, and chronic disorders (Stefanson & Bakovic, 2018). According to the findings of these research, falcarinol's ability to reduce inflammation may be useful in the treatment and prevention of disorders of the gastrointestinal tract or other systems.

#### 4.2.3. Ascorbic acid

Apart from being rich in provitamin A, carrots also rich in vitamin C (Char, 2018). Vitamin C is a water-soluble vitamin founded in various fruits and vegetables (Devaki & Raveendran, 2017). Vitamin C in carrots is available in the form of ascorbic acid. This vitamin also functions as an antioxidant by scavenging free radicals, thus improving oxidative stress conditions. Vitamin C exerts antioxidative activity by transferring electrons in both enzymatic and non-enzymatic processes to generate less reactive molecules (Akbari et al., 2016).

Ascorbic acid has antiviral properties, and a recent *meta*-analysis suggested that administering large doses of ascorbic acid relieved common cold symptoms and duration of sickness (Ran et al., 2018). An enhanced immune response and resistance against viral infections by increasing IFN-α/β was observed in the lungs infected with the Influenza A virus in vitamin C deficient mice after the intervention of sodium L-ascorbate (3.3 g/L) for 3 weeks (Kim et al., 2013).

As an antioxidant, ascorbic acid protected lymphocytes from oxidative impairment (Lenton et al., 1999). Supplementation of 1 g of ascorbic acid for 38 days also decreased the level of IgE and histamine in a swine model induced with soybean glycinin hypersensitivity, indicating a reduce in anaphylactic reactions (Sun et al., 2009). A review summarized another role of ascorbic acid in modulating the immune system is by influencing the functioning and growth of T lymphocytes and NK cells (Van Gorkom et al., 2018). Administration of 100 μM of vitamin C also regulated the cytokines by decreasing IFN-γ and TNF-α, as well as increasing the production of IL-10 in human lymphocytes *in vitro* model (Molina et al., 2014). At 48 and 72 h after ascorbic acid intervention, splenocytes of C57BL/6 mice induced by LPS or concavalin-A (con-A) showed an upregulation of anti-inflammatory cytokines such as IL-4 and IL-10, as well as downregulation in the expression of pro-inflammatory cytokines such as IL-6, IL-12, and TNF-α, indicating a decrease in pain caused by inflammation (Kong et al., 2015). Mechanism of ascorbic acid in reducing TNF-α and IL-6 production is also involving regulatory effects on the NFκB pathway by suppressing the production and signaling of ROS in NFκB transcription (Bowie & O'Neill, 2000; Cárcamo et al., 2002; Peng et al., 2005).

## 5. Challenges and future development

This review shows the potential of carrot has a huge variety of bioactive compounds that can be used as nutritional/therapeutic agents to modulate the immune system, either on inflammatory processes, antioxidant or redox balance, or on immune components in general. Nowadays, because of the escalating cost of immune therapy, natural medicines produced from plants are becoming more popular. Carrots, in particular, have a significant potential in the prevention or treatment of immune-related disorders due to their widespread availability and low cost. This suggests that developing carrot-based products, such as functional foods or supplements, might be a viable therapy for various immune-mediated diseases, metabolic disorders, inflammatory diseases, and infectious diseases.

However, there are several issues that must be addressed in future study. First, it is important to emphasize the study to characterize the specific phytochemical composition of carrots using established analytical methods and determine the best extraction methods to optimize the yield. The origin, plant identification and cultivation condition such as climate of the raw material (carrot) must be verified. Such parameters are essential in such research to produce replicable outcomes in pharmacological or clinical trials, enabling appropriate comparability. Though, many studies have yet to specifically examine the biochemical components of carrots for bioactive qualities such as antioxidant, anti-inflammatory, and immunomodulatory activity. It is recommended that analysis of bioactive components be used to evaluate the immunomodulatory activity of carrots, because, in this literature review, one of the bioactive chemical components that have been specifically identified for their effect on modulating the immune system is β-carotene and falcarinol.

Second, many studies used carrot interventions in the form of juice or extract and the use of isolated bioactive compound was still limited. This is a concern since it is difficult to determine which bioactive compounds have been shown to be effective in immunomodulatory pathways when utilizing an intervention in the form of a mixture. Specific bioactive compound identification can be used to prevent these misleading results. Then, in relation to experimental studies, it is crucial to extensively define the experimental procedures and compare the intervention with standard therapy in order to fully understand the effects of carrot's bioactive compounds on immune system modulation. Additionally, toxicological investigation is also necessary to ensure the continuity of clinical studies. Thus, further research was suggested to conduct Phase I to III clinical trials to determine the mechanisms, pharmacokinetics, safety and effectiveness of the immunomodulatory effects of carrots.

The ability of immune system to prevent diseases strongly influenced by the nutritional status of host. The discussion in this review suggested that the carrots can be used as a potent immunomodulator and when ingested could enhance the both cell-mediated and humoral immunity of host, either through their antioxidant or anti-inflammation properties. Carrots have the capacity to enhance the pharmaceutical, food, medical, and agricultural industries. Carrots are becoming increasingly popular as a result of increased public health awareness due to its high nutritional content and health advantages.

It has been explained that carrots contain bioactive compounds such as carotenoids, flavonoids, phenolic acids, polyacetylenes, and ascorbic acid, which have been proposed to have immunomodulatory effects; therefore, chemists may develop bioactive compounds isolated from carrots in the future. There has been a lot of development of genetically modified plant to enhance the amount of phytonutrients and biomarkers for dietary health, for example, red-fleshed apples rich in anthocyanins (Espley et al., 2013; Sekido et al., 2010), therefore researchers in this area of expertise such as biologists may develop genetically modified carrots high in β-carotene in order to enriched the nutritional benefit of carrots.

Nutraceuticals can be used as alternative supplementation in disease management as well as to maintain a healthy lifestyle. Carrot-based nutraceutical products enriched with β-carotene and antioxidant properties have been developed in the form of carrot-mix juice, carrot jam, and carrot candies (Riaz et al., 2022). Other carrot-based product development is also encouraged in order to create a more diverse functional foods, therefore it can reach a broader consumer target. Furthermore, carrot-based supplements can also be developed in

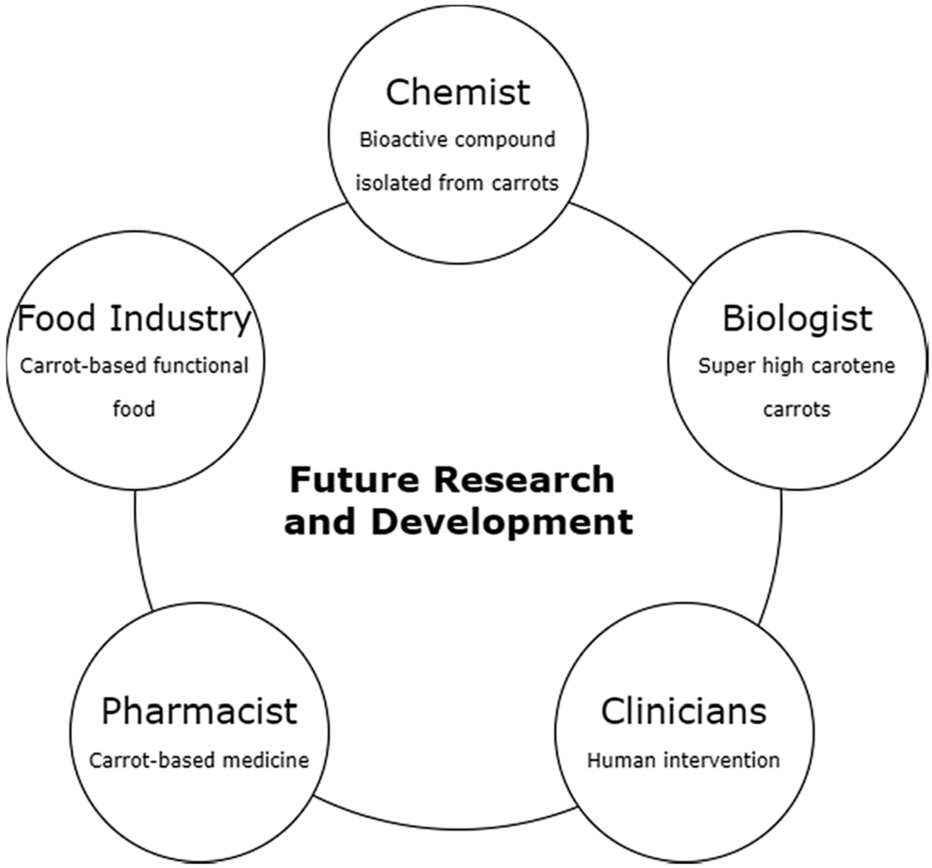


**Fig. 3.** Carrot's immunomodulatory effect future research and development.

pharmaceutical industry as single compounds or as phytocomplexes. Following pre-clinical and clinical research, carrot-based supplements or nutraceuticals can be used as human interventions as a complementary treatment in immune-related diseases.

Therefore, future collaborations between researchers in various fields such as chemists, biologists, clinicians, and pharmacists as well as food industry are needed for further exploration regarding the influence of carrots on the human immunity (Fig. 3). Collaboration between researchers and industry can be a benefit in order to fasten the discoveries of this vegetable's benefits.

## 6. Conclusion

Carrot bioactive compounds such as β-carotene, phenolic acids, flavonoids, polyacetylenes, and ascorbic acid were found to have immunomodulatory activities via anti-inflammatory, antioxidant, and immune system pathways. On the anti-inflammatory pathway, the bioactive substances in carrots inhibition of pro-inflammatory responses and improvement of the anti-inflammatory cytokine levels, and promoted signaling pathways related to inflammation prevention. On the antioxidant pathway, carrots' bioactive substances carrots ameliorated oxidative stress by eliminating ROS and thus reduced oxidative stress parameters, increased antioxidant enzymes and oxidative stress prevention mechanism to achieve an improvement in antioxidant status. Immunomodulating effects of carrots also included the regulation of antibodies, leukocytes, immunoglobulins and histamine.

β-carotene is one of the most commonly encountered provitamin A and was abundant in carrots. β-carotene acts as an immunomodulator by regulating leukocyte formation and activity, enhancing immunoglobulin production, modulating inflammatory cytokine release, and decreasing pro-inflammatory mediators. One of the ways β-carotene controls the immune system is through redox balance alterations related to lipid peroxidation and antioxidant enzymes.

These immunomodulatory characteristics is one of the efforts to maintain the balance of immune response and oxidant-antioxidant status in the body. Thus, it could be suggested that carrots have the potential to maintain the optimal immunity. Many studies have yet to precisely study carrot's biochemical components for bioactive properties such as antioxidant, anti-inflammatory, and immunomodulatory activity. Collaborative works are suggested to further investigate bioactive components as well as underlying processes, specifically carrot immunomodulatory action and future accessability of carrot-based products.

## CRediT authorship contribution statement

**Gemala Anjani:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Funding acquisition. **Fitriyono Ayustaningwarno:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Rafika Eviana:** Methodology, Formal analysis, Investigation, Data curation, Writing – original draft.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gemala Anjani reports financial support was provided by The Ministry of Education, Culture, Research, and Technology of Indonesia.

## Data availability

No data was used for the research described in the article.

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