ISSN 2406-8233

BIOLEARNING JOURNAL
ISSN: 2406-8233; EISSN; 2406-8241 Volume 10 No. 2. Juli 2023

Review

PLANT BIOACTIVE ; CAROTENOIDS, POLYPHENOLS AND FLAVONOIDS IN IMPROVING THE IMMUNE SYSTEM AGAINST COVID-19 INFECTION

James Ngginak[1,*], Sonya T.M. Nge[2], Tiodor S. J. Manalu[3], Paulus D.B. Murti[4],Yanti Daud[5]

[1,2,5] Biology education study program Artha Wacana Christian University Kupang, NTT Indonesia
[3]High school Unggul Del North Sumatera, Indonesia
[4]Karangturi University Semarang, Indonesia
Correspondence : email jamesngginak@ukaw.ac.id

ABSTRACT

COVID-19 (coronavirus) is a new type of virus that can cause disease in animals and humans. This type of virus causes a crisis or threat to human life in 2020. Before an ideal vaccine or drug is found to prevent COVID-19 infection, steps or approaches are needed that can break the chain of infection. Several things that can be done to prevent COVID-19 infection are to take advantage of the chemical content of natural ingredients, maintain nutritional intake, maintain the resilience of the body's immune system and adhere to health protocols. The public needs to be made aware of the use of natural metabolites in order to maintain the body's defense system. Carotenoids, polyphenols and flavonoids are a group of secondary metabolites in plants that can physiologically increase the body's immune system against bacterial and viral infections. Red, yellow pigments in plants and some organisms known as coarotenoids have the ability to enhance the body's immune response or cellular immune system. While polyphenols and flavonoids are a unique group of phytochemicals in fruits, vegetables and herbs. This component has the potential to inhibit viral replication. People are expected to use plant chemical compounds to improve the body's immune system.

Keywords : Metabolism, variant, host, mutation, active compound

1. Introduction

Corona virus diseases-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of virus that infects the human respiratory system. This type of virus has become a pandemic virus that affects various sectors of human life in the world such as the economy, health, food security and even causes death so that it becomes a worrying issue or event in 2020 (Zhang & Liu, 2020). In this regard, the world community and the world health organization (WHO) are thinking about preventing the COVID-19 pandemic. In addition to following the government's recommendations, some efforts that can be done in order to reduce infections are the discovery of vaccines. The discovery of vaccines will certainly take time because the vaccines that are found need to be tested for safety and effectiveness before being used by humans. On the other hand, ordinary people think that one of the solutions to prevent the COVID-19 pandemic is through the use of generic drugs. People believe that the use of certain drugs can inhibit or stop the spread of COVID-19. However, the public needs to be aware and understand that the improper and correct use of generic or polypharmacy drugs can cause side effects for the body (Destiani & Susilawati, 2013). Even some people think that alcohol consumption is one solution in preventing infection with the corona virus dieases-19. In a situation like this, of course, personal preventive measures are needed to prevent the increasingly widespread spread of COVID-19.

In this article, the author describes the potential use of secondary metabolites in plants that can improve the immune system against viral infections. Everyone can maximize secondary metabolite compounds sourced from organisms such as spices or natural materials that are cultivated around the house or garden. According to Bria et al (2019), herbs or spices contain secondary metabolites that are good for body health. Carotenoids and polyphenols are two of the many secondary metabolites that can physiologically and pharmacologically improve the work of the body's immune system against bacterial and viral infections (Anunciato et al, 2012). Red, yellow pigments in plants known as carotenoids, have the ability to increase the body's immune response or cellular immune system (Ngginak et al, 2020). Carotenoids are known to reduce the immunosuppressive effect of UV light and can inhibit enzymatic reactions between body cells and viruses or the productivity of viral genetic material (Santoyo et al, 2012). Based on the study data, it was found that -Carotene supplementation was able to significantly modulate the immune system against viral attacks by changing the percentage of T and B cell subsets (Toti et al, 2018). Carotenoid components can also stimulate the proliferation of B and T lymphocytes, increase macrophage activity and cytotoxic T cell function and cytokine production (Milani et al, 2017). According to Cicero & Coleti (2017) astaxanthin significantly increases the phagocytosis and

ISSN 2406-8233

BIOLEARNING JOURNAL
ISSN: 2406-8233; EISSN; 2406-8241 Volume 10 No. 2. Juli 2023

microbicidal capacity of neutrophils and can increase the intracellular calcium concentration.

While polyphenols and flavonoids are a unique group of phytochemicals in fruits, vegetables and herbs. This component has great health potential through the mechanism of neutralization of free electrons and the ability to inhibit viral replication. Herbacetin, isobavachalcone, quercetin 3 d gluc glucoside helichrysetin in the body can inhibit the enzymatic activity of MERS CoV 3CLpro (Jo et al, 2019). Studies related to the role of flavonoids with silymarin type have a spectrum of antiviral activity that is able to block the replication of influenza A virus (Lani et al, 2015). One member of the polyphenols, namely catechins, has the activity of inhibiting the work of the influenza A virus by binding to hemagglutinin and limiting virus adsorption and preventing virus penetration into cells (Qaddir et al, 2017). In addition, flavonoids are able to inhibit the work of viruses in various mechanisms such as preventing the attachment or entry of viruses into host cells and blocking viral transcription and replication (Lalani & Chit 2020). It can be said that the components of secondary metabolites are able to prevent the intervention of viral protein molecules against body cells. The very fast mutation factor of COVID-19 (Delta and Omicron) needs attention so that preventive measures through the use of active compounds of natural ingredients are appropriate and appropriate.

2. Carotenoids and the Immune System

Carotenoids are a type of natural pigment that plays a role in the process of photosynthesis. According to Prianti et al, (2014) this group of dyes is present as accessory pigments that play an important role in harvesting light for the photosynthetic needs of green plants. Chlorophyll is assisted by carotenoids in regulating or selecting sunlight needed for photosynthesis. In line with that, Jaswir et al., (2011) also explained that Carotenoids are known as pigments that help harvest light for phytochemical reactions and protect chlorophyll from harmful rays (photoprotectors). The colors yellow, orange and red are the identities of the widely distributed carotenoids in plants. This group of pigments is generally responsible for the color of leaves, fruit and flowers of plants and the color of several organisms such as fungi, fungi, crustaceans and bacteria (Zeb & Mehmood, 2004).

Based on their properties, carotenoids are divided into two groups, namely carotenes (having hydrocarbon groups such as -carotene, β-carotene, ψ-carotene (γ-carotene), and lycopene) and xanthophylls (having hydroxy groups such as lutein, cantaxanthin, β-cryptoxanthin, lutein, zeaxanthin, astaxanthin, fucoxanthin and peridinin). More than 800 types of carotenoids have been found with geometric isomeric structures (trans and cis). Several types of them have potential for human health (Maoka, 2020). Carotenoids are composed of a tetraterpenoid C40 chain formed from eight C5 isoprenoid units. This structure forms a symmetrical framework that has lateral methyl groups separated by six C atoms at the center and five C atoms elsewhere. This modification of the chain structure makes carotenoids have hydrogenation, dehydrogenation and extension properties. Carotenoids are produced from isopentenyl pyrophosphate (IPP) components which undergo a gradual process to form various types of carotenoids (Britton et al, 2009). Typical molecular chain characteristics such as conjugated double bonds are able to absorb light and form chromatophores which are responsible for the yellow, orange, or red colors in foodstuffs (Toti et al, 2018). Carotenes exhibit considerable structural diversity, including different carbon bonds, double bond equivalence levels and bond cyclization (Milani et al, 2017). According to Christaki et al (2013), carotenoids are known as a group of isoprenoid molecules synthesized by green plants, fungi, algae and bacteria. Some xanthophylls are present as fatty acid esters, glycosides, sulfates and protein complexes. The xanthophyll structure shows marked diversity. Most carotenoids have a 40-carbon skeleton. Some carotenoids have a 45 or 50 carbon skeleton. Such a carbon chain structure causes this compound to be easily oxidized but also has good biological power or function (Maoka, 2020). Understanding the relationship between the structure, properties, and function of carotenoids is very important because in the context of biology it helps to design and optimize the use of these compounds for commercial purposes. The chemical structure of several types of carotenoids can be seen in the following figure.

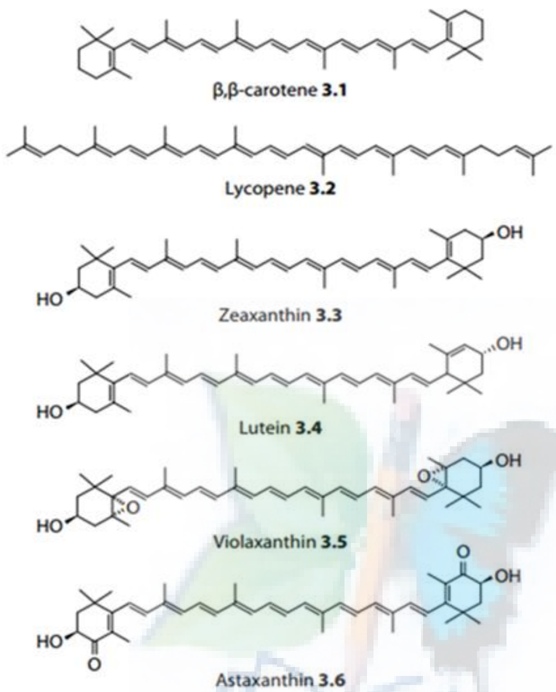

Figure 1. Chemical structure of several types of carotenoids (Landrum, 2010)

The carotenoid pigment group is a tetrapenoid compound that can be found in photosynthetic bacteria, several species of archaea, fungi, algae, plants and animals (Maoka, 2020). Plant organs where carotenoids accumulate are fruits, roots, seeds, flowers and leaves. While in animals this compound can be found in eggs, meat and shells. Generally, animals cannot synthesize carotenoids on their own. The accumulation of carotenoids in the animal body occurs through food intake (Ngginak et al, 2017). According to Vilchez et al (2011), carotenoids are natural pigments that can be synthesized by all photosynthetic organisms and fungi. In line with that, according to Collins et al (2011), carotenoids are tetrapenoid pigments that can naturally be found in all photosynthetic organisms, some bacteria, fungi and some animals.

In green plants, carotenoids act as accessory pigments that form red, yellow and orange colors. This group of pigments also helps the process of absorbing light for the photosynthesis mechanism of green plants as well as protecting plants against harmful sunlight (Maoka, 2020). According to Milani et al, (2017) the composition of chemical compounds in plants can be used as a form of self-defense against predators or extreme environmental conditions. Britton et al (2008), stated that carotenoids are accessory pigments that help in the process of photosynthesis as well as basic structural units involved in the photosynthesis mechanism. This group of pigments also acts as a photoprotector against harmful light and gives flowers and fruit different colors. The photoprotection mechanism of Carotenoids includes quenching the chlorophyll triplet state so as to prevent the formation of singlet oxygen which can oxidize chlorophyll. In addition, Carotenoids are also able to prevent the formation of singlet oxygen directly.

Carotenoids that accumulate in the body of animals act as a mating signal, a form of body defense against predators, as a signal for sex status, as a substance to increase the animal's immune system (Ngginak et al, 2017). Along with the development of science and technology, the application of carotenoids in human life has developed well. According to Anunciato (2012), Carotenoids have been applied in the cosmetics, food, medicine and animal feed industries. Commercially, carotene has been used as a feed additive, animal feed supplement, natural food coloring, nutritional supplement, for cosmetic and pharmaceutical purposes (Jaswir et al., 2011). Novoveska et al (2019), explained that carotenoids have practically been applied in the food, feed, cosmetic and nutraceutical industries because they have strong antioxidant properties. The medical world uses carotenoids as medicines to prevent degenerative, acute and chronic diseases. According to Britton et al (2008) carotenoids can act as photoprotection such as inhibiting lipid peroxidation and preventing DNA damage and increasing the immune system response. Jaswir et al (2011) also suggested that carotenoids can prevent degradative ocular disease as well as antioxidants, anticancer, anti-obesity, prevent heart disease and osteoporosis (Rao & Rao, 2007). According to Pesang et al (2020) this group of compounds has biological activities as anti-oxidants, anti-cancer, anti-obesity, anti-diabetes, anti-inflammatory, anti-tumor, anti-bacterial and protective organs in the body. Chlorophyll and Carotenoids have good development prospects for the pharmaceutical, food and cosmetic industries (Ginting et al, 2018).

The immune system is a form of body defense that is formed in order to anticipate various disease attacks. According to Zhang & Liu (2020), this form of body defense consists of two kinds, namely innate and adaptive forms of defense. Truly effective defense of the immune system is based on a balance of the entire immune system. The response of the human immune system is complex and carotenoids have been reported to have positive effects in maintaining the balance of the immune system. An understanding of the immune system is not just an ordinary understanding, but it is necessary to understand basic biological concepts (physiology, immunology and molecular biochemistry). Under normal circumstances the immune system response can be hyperactive, which is a condition in which the disease is mediated by the immune system. While the hypoactive response that causes suppression of immunity and the inability of the immune system to disease.

Immune cells are highly active cells and therefore can produce reactive oxygen species (ROS) during normal cell activities. The mitochondrial electron transport system uses about 85% of the oxygen consumed by cells to produce ATP. Thus, mitochondria are organelles that have a high potential to generate ROS (Milani et al. 2017; Christaki et al., 2013; Ucci et al., 2018).

The presence of carotenoids in mitochondria has relevance. Carotenoids can function to protect subcellular organelles of immune cells from the adverse effects of oxidative reactions. The optimal function of subcellular organelles is to ensure that cellular functions including apoptosis, cell signaling and gene regulation run normally. Research by Boon & Jean (2004) explained that the induction of carotenoids (lutein, astaxanthin and -carotene) in cats and dogs showed high levels of carotenoid accumulation in mitochondria, nucleus, microsomes and lymphocytes. Therefore, it is recommended to consume foods that contain carotenoids such as vegetables and fruit. Consumption of vegetables and fruit can help boost the immune system. when the immune system is formed properly then oxidative reactions that are damaging can be neutralized. This mechanism may enhance cell-mediated immune responses. Oxidative reactions can also be triggered by the consumption of foodstuffs contaminated with heavy metals, chemicals, foods that are high in fat, fried foods, roasting (burnt), due to air pollution.

In anticipating the body's oxidative reactions, the steps that can be taken are to arrange a balanced lifestyle by consuming self-processed food ingredients,

ISSN 2406-8233
BIOLEARNING JOURNAL
ISSN: 2406-8233; EISSN; 2406-8241 Volume 10 No. 2. Juli 2023

while also reducing the processing and consumption of fried foods, not smoking, and exercising regularly.

The ability of carotenoids to modulate the immune system begins early in embryonic development (ontogenesis). Research by Toti et al (2018), explained that β-Carotene supplementation significantly changed the percentage and total number of splenic CD3 + cells, CD4 + and CD8 + and IgG production in mice. Lycopene also increases the number of a subset of T and B cells. In humans, the sequence of events for developing T lymphocytes begins during embryogenesis. Supplementation with -carotene stimulates lymphocyte proliferation. Adult humans who were given β-carotene orally had an increase in the number of Th and T lymphocytes. However, there is something interesting about the administration of carotenoid supplements that the age factor greatly affects the body's bioavailability in increasing the immune system response. Giving carotenoid supplements through food at an early age of up to 45 years shows a better immune response than people over the age of 45 who show an unstable immune response (Michelle et al, 1997).

In another study, administration of astaxanthin to healthy young women stimulated mitogen-induced lymphoproliferation and increased cytotoxic activity of NK cells. Astaxanthin also increases the total number of T and B cells. Astaxanthin has also been shown to reduce DNA damage in the acute phase. The results of trials on mice showed that lutein and astaxanthin increased the antibody response of splenocytes to T-cell antigens (Toti et al, 2018).

According to George et al (1997), dietary β-carotene, lutein or astaxanthin stimulates DTH responses, CD4+ Th cell counts and IgG production. Supplementation with astaxanthin, β-carotene or lutein also showed higher DTH, Th and B responses and increased plasma IgG concentrations. These results suggest that β-carotene, lutein and astaxanthin may have immune enhancing activity. However, it is important to know that immune response factors can be modulated specifically based on the type of carotenoid given and the species being tested. Astaxanthin stimulates the proliferation of lymphocytes, increases the total number of antibody-producing B-cells, results in an increase in the number of T-cells and enhances the cytotoxic activity of natural killer cells. This compound significantly increases the delayed-type hypersensitivity response and dramatically reduces DNA damage (Boon & Jean 2004; Capelli & Cysewski 2010). Mice given β-carotene, canthaxanthin, or astaxanthin showed an increase in toxic T cells.

Viruses are obligate intracellular parasites, containing little more than a few strands of RNA or DNA genes and containing lipids (Wagner et al, 2007). But viruses are very simple organisms. The mechanism of action of viruses is to utilize the environment of the host cell to produce new viruses. Viruses use the cells they invade to produce many viral cells that cause disease in the body.

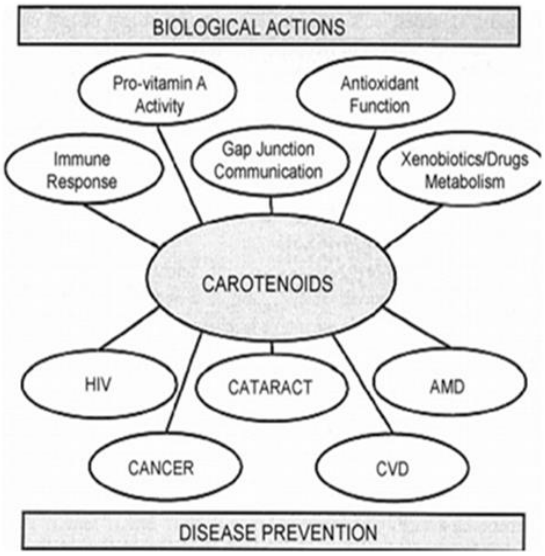

Figure 2: The role of carotene in chronic disease prevention (Rao and Rao 2007)

Viruses have many invasion strategies. According to Wagner et al (2007). Each viral strain has a unique surface molecular configuration. These surface molecules work like keys and locks. Viruses are possible to enter the host through the mechanism of precision locks and locks. In other words, the virus will reproduce if the virus molecule will determine its exact position on the target cell membrane so that a match is formed. The success of the virus infecting is influenced by four factors, namely genetic variation, variations in the mode of transmission, efficient replication in host cells and the ability to survive in the host. As a result, if the virus has adapted to all biological systems and has occupied many ecological niches, it causes widespread disease in humans, livestock and plants (Damayanti & Panjaitan, 2014).

Viruses are microorganisms that cannot live alone like bacteria. Therefore, in order to live, viruses need a host cell to replicate. The process of replication occurs by riding the normal cellular metabolic pathways. Thus, it is difficult to trace and treat virions directly or by replicating them (Delshadi et al, 2021). Various breakthroughs can be made to disrupt the activity of viral enzymes as locks seeking partners. Viral enzymes have a key role in triggering disease. If the viral enzymes are neutralized then the infection can be controlled. The proteolytic process of viral polyprotein precursors by viral proteinases is essential for viral maturation. Thus designing specific inhibitors for each viral protease is effective for controlling viral infection. Chemical compounds from natural ingredients are able to inhibit viral DNA and RNA replication (Wagner et al, 2007).

ISSN 2406-8233

BIOLEARNING JOURNAL
ISSN: 2406-8233; EISSN; 2406-8241 Volume 10 No. 2. Juli 2023

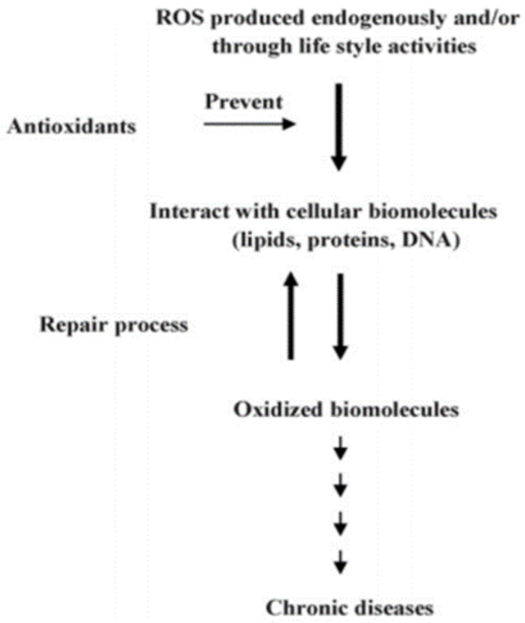

Figure 2: The role of carotene in chronic disease prevention (Rao and Rao 2007).

In Jassim & Naji (2003), it was reported that the polysaccharides extracted from the leaves of Rhizophora apiculata and the bark of Rhizophora mucronata had an inhibitory effect on the action of the virus. MT-4 cells from both samples were protected from cytopathogenicity and HIV antigen-induced blocking of p24 (viral capsid protein). The active compounds in the samples could prevent the binding of the virus into cells after cultivation of MOLT-4/HIV-1IIIB cells and MOLT-4 cells. According to Lewis et al (2013), extracts of chemical compounds from Aloe barbadensis can increase the concentration of anti-CVB3 antibodies. The data conclusively show that Aloe polimannose can enhance immunopotentiate against the production of immature capsid protein epitope antibodies from picornavirus. Biological response of Aloe polimannose can increase the concentration of antibodies against enterovirus. These compounds block the virus and prevent a productive infection cycle so that the viral genome will not be inserted into the cell (Wagner et al, 2007).

Feeding carotenoid-based diets to mice induced with aflatoxin B1 (AFB1) showed that carotenoids (β-carotene, b-apo8'-carotene, astaxanthin and canthaxanthin) were highly efficient in reducing the number and size of liver preneoplastic or liver DNA damage in mice. The carotenoid detoxification pathway will convert AFB1 into aflatoxin M1 which is less genotoxic. Carotenoids are also able to reduce the carcinogenic activity of AFB by increasing detoxification by increasing the glutathione S-transferase response, which catalyzes flapoxin-8,9-epoxide. Carotenoids, canthaxanthin, astaxanthin and -apo-8-carotenal induced in mice may also inhibit the initiation of hepatic preneoplasias by AFB1 by activating the CYP1A gene (Boon & Jean, 2004). Carotenoid supplementation can influence cell growth, modulate gene expression and immune response. Carotenoid components can stimulate the proliferation of B and T lymphocytes, increase macrophage activity and cytotoxic T cell function and cytokine production (Milani et al, 2017).

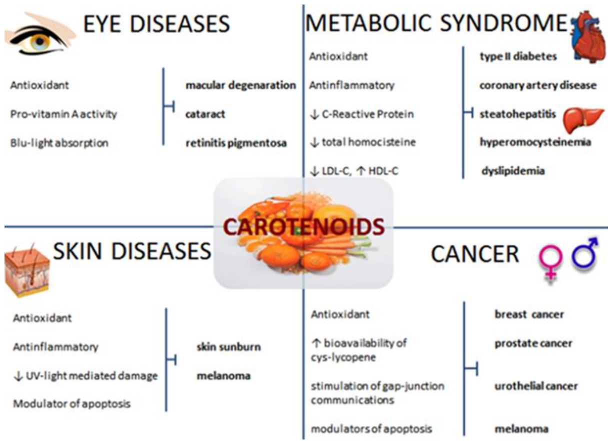

Figure 4. Benefits of carotenoids. Source : Cicero & Coleti (2017)

3. Curcuminoids and the Immune System

Curcuminoid is a yellow dye known as curcumin. According to Srivastava et al (2011), curcumin is known as a phytochemical (1,7-bis (4-hydroxy-3-methoxyphenyl)1,6-heptadiene 3,5-dione). These compounds can be obtained from plants such as turmeric and ginger. Curcumin has benefits as an anti-cancer, anti-proliferative, anti-carcinogenic skin, colon cancer, breast and liver. Curcumin compounds also have anti-oxidative, anti-inflammatory and antiseptic effects (Salvioli et al 2007).

Curcumin also acts as a safe and powerful immunomodulator. These compounds are able to form a strong immune system and also modulate adaptive immunity by increasing T-cell proliferation (Varalakshmi et al., 2008). Curcumin (diferuloylmethane) can inhibit the cellular mitagenic response of epithelial cells (Sharma et al., 2007). Curcumin is one of the compounds that have good pharmacological abilities for the body such as anti-inflammatory, antioxidant, anticancer, antiapoptotic and anti-oxidative. This compound is also able to inhibit the activity of the influenza virus by inhibiting the attachment of viral cells to host cells. The test results through pre-incubation of the virus with curcumin showed the presence of influenza virus plaque inhibition (Fioravanti et al, 2012).

Polyphenols are one of the secondary metabolic compounds synthesized through glucose metabolism. This group of compounds has a hydroxyl group on the benzene ring which acts as an antioxidant (Padamani et al, 2020). This organic compound has more hydroxyl groups attached to the phenyl ring. Polyphenols are not involved in the normal growth and development of plants but play an important role in plant defense mechanisms against viruses, bacteria, fungi and herbivores. Polyphenols are synthesized from phenylalanine or tyrosine (Papuc et al, 2017). Other compounds that have anti-viral capacity are flavonoids. Flavonoids can be divided into different subgroups depending on the C ring carbon, the position of the B ring, the degree of unsaturation and the oxidation nature of the C ring. If the B ring is in position 3 of the C ring, it is called an isoflavone. Ring B linked at position 4 is called neo flavonoid, while ring B linked at position 2 can be further subdivided into several subgroups such as avones, avonols, avanones, avanonols, avanols or catechins, anthocyanins and chalcones (Panche et al, 2016). Saponins are also a secondary metabolic compound that has an important role in preventing viral and bacterial infections in the body through the mechanism of increasing body resistance (Ngginak et al, 2021: Seko et al, 2021).

3. Curcuminoids and the Immune System

Curcuminoid is a yellow dye known as curcumin. According to Srivastava et al (2011), curcumin is known as a phytochemical (1,7-bis (4-hydroxy-3-methoxyphenyl)1,6-heptadiene 3,5-dione). These compounds can be obtained from plants such as turmeric and ginger. Curcumin has benefits as an anti-cancer, anti-proliferative, anti-carcinogenic skin, colon cancer, breast and liver. Curcumin compounds also have anti-oxidative, anti-inflammatory and antiseptic effects (Salvioli et al 2007).

Curcumin also acts as a safe and powerful immunomodulator. These compounds are able to form a strong immune system and also modulate adaptive immunity by increasing T-cell proliferation (Varalakshmi et al., 2008). Curcumin (diferuloylmethane) can inhibit the cellular mitagenic response of epithelial cells (Sharma et al., 2007). Curcumin is one of the compounds that have good pharmacological abilities for the body such as anti-inflammatory, antioxidant, anticancer, antiapoptotic and anti-oxidative. This compound is also able to inhibit the activity of the influenza virus by inhibiting the attachment of viral cells to host cells. The test results through pre-incubation of the virus with curcumin showed the presence of influenza virus plaque inhibition (Fioravanti et al, 2012).

.

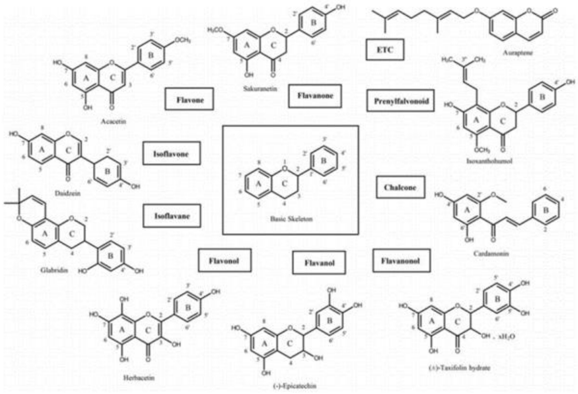

Figure 4. The basic structure or framework of Flavonoids and their classes (Jo et al, 2020)

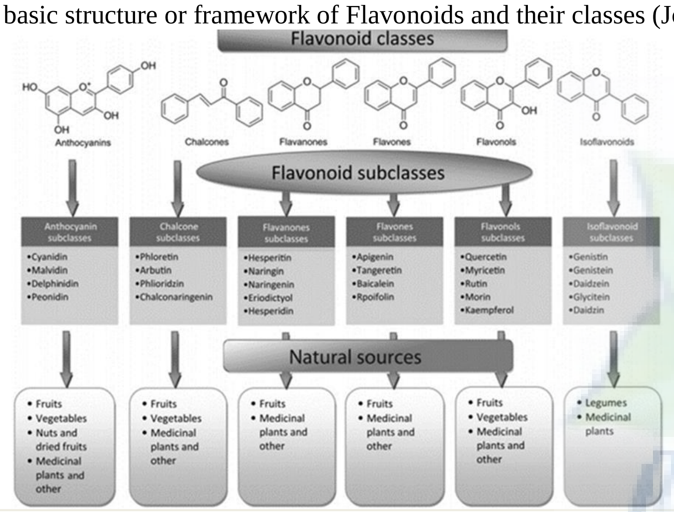

Figure 5. Flavonoid class, sub class and natural source (Panche et al, 2016)

4. Polyphenols, Flavonoids and the Immune System

Polyphenols are one of the secondary metabolic compounds synthesized through glucose metabolism. This group of compounds has a hydroxyl group on the benzene ring which acts as an antioxidant (Padamani et al, 2020). This organic compound has more hydroxyl groups attached to the phenyl ring. Polyphenols are not involved in the normal growth and development of plants but play an important role in plant defense mechanisms against viruses, bacteria, fungi and herbivores. Polyphenols are synthesized from phenylalanine or tyrosine (Papuc et al, 2017). Other compounds that have anti-viral capacity are flavonoids. Flavonoids can be divided into different subgroups depending on the C ring carbon, the position of the B ring, the degree of unsaturation and the oxidation nature of the C ring. If the B ring is in position 3 of the C ring, it is called an isoflavone. Ring B linked at position 4 is called neo flavonoid, while ring B linked at position 2 can be further subdivided into several subgroups such as avones, avonols, avanones, avanonols, avanols or catechins, anthocyanins and chalcones (Panche et al, 2016). Saponins are also a secondary metabolic compound that has an important role in preventing viral and bacterial infections in the body through the mechanism of increasing body resistance (Ngginak et al, 2021: Seko et al, 2021)

Flavonoids are useful as antioxidants, antiatherogenic, anticancer, anti-inflammatory, antimicrobial and anti-infective (Moradi et al, 2019). Flavonoids also have anti-oxidative, anti-inflammatory, anti-mutagenic, heart disease-preventing and anti-carcinogenic properties. The polyphenol and flavonoid compounds have the ability to inhibit the work of several enzymes such as xanthine oxidase cyclo-oxygenase, lipoxygenase and phosphoinositide 3-kinase (Panche et al, 2016). Flavonoids are now considered as indispensable components in various nutraceutical, pharmaceutical, medicinal and cosmetic applications. Polyphenols are not involved in the normal growth and development of plants but have an important role in plant defense mechanisms against viruses, bacteria, fungi and herbivores (Sayuna et al, 2020). Flavonoids are a group of natural substances with a phenolic structure found in fruits, vegetables, seeds, bark, roots, stems, flower plants, tea and grapes (Panche et al, 2016).

Research using flavonoid extract is reported to inhibit viral DNA synthesis. Types of flavonoids such as quercentin and myricetin have shown inhibitory activity against cellular DNA replication or viral RNA polymerase. Plant polyphenols have a positive impact on human health such as reducing oxidative processes, inhibiting the growth of bacteria, viruses and fungi (Papuc et al, 2017). Research conducted by Fioravanti et al (2012) explains that polyphenols have the ability to inhibit influenza virus replication in accordance with the dose given. Polyphenol molecules are able to inhibit the intracellular pathway of viral replication. The action of MAP kinase is able to control the activity of the core-cytoplasmic ribonucleoprotein complex of the virus. Intake of polyphenols such as resveratrol [5-(1E)-2-(4- hydroxyphenyl)ethenyl]-1,3-benzenediol (red wine) and curcumin [diferuloyl methane; 1,7-bis-(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione] (curry powder) has anti-cancer, anti-inflammatory and anti-viral benefits. One of the polyphenolic compounds, namely ribovlavone, has been shown to have the ability to inhibit virus replication based on in vitro tests on mice.

Research conducted by Moradi et al (2019), shows that polyphenol extracts from pomegranate have antiviral activity. The active compounds contained can inhibit the replication of the influenza virus. According to Lalani & Chit (2020), these compounds can block the entry of viruses into cells, while also interfering with various stages of the viral replication process and preventing the release of viral DNA in order to infect other cells. Flavonoids that inhibit viral activity through the mechanism of interaction with virus-specific extracellular regions such as viral proteins in the capsid. In addition, flavonoids are able to inhibit the work of viruses such as preventing the attachment or entry of viruses into host cells, modifying the structure of the virus, inhibiting the uncoating of viruses, inhibiting early-stage replication, blocking transcription and replication, inhibiting the final stages of maturation such as packaging and release, interfering with receptor factors. necessary for successful infection (Lalani & Chit 2020).

Polyphenol derivatives such as ginkgetin inhibit the sialidase activity of the influenza A virus (inhibit viral assembly and release) (Miki et al, 2007). Luteolin compounds can also inhibit the entry of influenza viruses that can cause respiratory syndrome (SARS-CoV). This compound will interact with influenza A virus hemagglutinin and SARS CoV virus S2 protein through a modulating mechanism (Schwarz et al, 2014).

In a study by Nagai et al (1995), it was explained that other groups of flavonoids such as methoxyflavone, isoscutellarein, and 8-methoxy-isoscutellarein were able to inhibit the initial replication of influenza A virus by reducing sialidase activity, inhibiting lysosomal fusion and RNA polymerase activity. Other types of flavonoids such as silymarin have a spectrum of antiviral activity capable of blocking the replication of influenza A virus (Lani et al, 2015).

One of the flavonoid members, namely catechins, has the activity of inhibiting the work of the influenza A virus by binding to hemagglutinin and limiting virus adsorption and preventing virus penetration into cells (Qaddir et al, 2017). Flavonoid catechins have also been reported to inhibit the replication of influenza A and B viruses by acidification in the surrounding lysosomes and endosomes through clathrin-mediated endocytosis (Imanishi et al, 2002). In addition to having influenza antiviral activity, flavonoids, such as epigallocatechin gallate (EGCG), have been shown to actively bind to CD4+ T cells. Epigallocatechin gallate also inhibits hepatitis B virus (HBV) replication by interfering with the production of pre-nuclear mRNA and DNA replication intermediates (He et al, 2011). Zika virus is also inhibited by EGCG, because it is able to interact with lipid membranes and block the entry of the virus into cells (Carneiro et al, 2016).

Polyphenols and flavonoids are a group of compounds that have the potential to improve the body's immune system. Herbacetin, isobavachalcone, quercetin 3-β-d-glucoside and helichrysetin were found to block the activity of the MERS-CoV 3CLpro enzyme. Experimental and computational studies show that flavonols and chalcone are potential chemical structures that can modulate and bind to the MERS-CoV 3CLpro catalytic site (Jo et al, 2019).

5. Conclusion

COVID-19 (coronavirus) is a type of virus that can cause disease in animals and humans. Some things that can be done or help control COVID-19 infection are to take advantage of the chemical or bioactive content found in plants such as carotenoids, polyphenols and flavonoids. Chemically, the types of compounds contained in plants have the ability to increase the immune system.

5. References

1. Anunciato, T.P., da Rocha, Filho. PA. (2012). *Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals*. Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Brasil. (51-53)
2. Bria. H., Sabuna, A., Ngginak. J., Hendrik. Ch. A. (2019). Tumbuhan Berkhasiat Obat Untuk Kesehatan Reproduksi Di Desa Umalor Kecamatan Malaka Barat Kabupaten Malaka. *Media Farmasi Indonesia*, *14*(Vol 14 No 1 (2019): Media Farmasi Indonesia), 1493–1499. https://stifar.ac.id/ojs/index.php/MFI/article/view/110
3. Britton, G., S.L. Jansen and H. Pfander. (2008). Carotenoids. Volume 4. Natural Functions. Basel, Switzerland ritton, G., S.L. Jansen and H. Pfander. (2008). Carotenoids. Volume 4. Natural Functions. Basel, Switzerland
4. Britton G, Liaaen-Jensen S, Pfander, H (2009) Carotenoids volume 5: nutrition and health, Birkhäuser: Basel, Switzerland.
5. Boon P. Chew, & J. S. P. (2004). Functions and Actions of Retinoids and Carotenoids: Building on the Vision of James Allen Olson: Foreword. *Journal of Nutrition*, *134*(1), 257–261.
6. Capelli, Bob & G.R. Cysewski. (2010). Potential Health Benefits of Spirulina Microalgae. Nutra Foods 9 (2) : 19-26.
7. Carneiro, B.M.; Batista, M.N.; Braga, A.C.S.; Nogueira, M.L.; Rahal, P. (2016). *The green tea molecule EGCG inhibits Zika virus entry. Virology*. 496, 215–218. [CrossRef]
8. Cicerostaki, E., & Bonos, E. (2013). *Functional properties of carotenoids originating from algae*. *August 2012*. https://doi.org/10.1002/jsfa.5902
9. Cicero, A. F. G., & Colletti, A. (2017). Effects of Carotenoids on Health: Are All the Same? Results from Clinical Trials. *Current Pharmaceutical Design*, *23*(17).https://doi.org/10.2174/1381612823666170207095459
10. Collins, A. M., Jones, H. D. T., Han, D., Hu, Q., Beechem, T. E., & Timlin, J. A. (2011). Carotenoid distribution in living cells of haematococcus pluvialis (chlorophyceae). *PLoS ONE*, *6*(9), 1–8. https://doi.org/10.1371/journal.pone.0024302
11. Damayanti, T. A., & Panjaitan, M. T. (2014). Aktivitas Antivirus Beberapa Ekstrak Tanaman Terhadap Bean Common Mosaic Virus Strain Black Eye Cowpea (Bcmv-Bic) Pada Kacang Panjang. *Jurnal Hama Dan Penyakit Tumbuhan Tropika*, *14*(1), 32–40. https://doi.org/10.23960/j.hptt.11432-40
12. Delshadi, R., Bahrami, A., Mcclements, D. J., Moore, M. D. & Williams, L. (2021). Development of nanoparticle-delivery systems for antiviral agents: A review. J Control Release, 331, 30-44
13. Destiani D. P., Susilawati. (2013). Peresepan Obat Pasien Penyakit Dalam Menggunakan Indikator Peresepan *World Health Organization.* Jurnal Farmasi Klinik Indonesia Volume 2, Nomor 4. Indonesia.
14. Fioravanti, R., Celestino, I., Costi, R., Cuzzucoli Crucitti, G., Pescatori, L., Mattiello, L., Novellino, E., Checconi, P., Palamara, A. T., Nencioni, L., & Santo, R. Di. (2012). Effects of polyphenol compounds on influenza A virus replication and definition of their mechanism of action. *Bioorganic and Medicinal Chemistry*, *20*(16), 5046–5052.https://doi.org/10.1016/j.bmc.2012.05.062
15. George. W. Comstock, A. E. Burke, S. C. Hoffman et al., (1997) "*Serum concentrations of α tocopherol, β carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus*," Annals of the Rheumatic Diseases, vol. 56, no. 5, pp. 323–5,
16. Ginting, N. K., Sedjati, S., Supriyantini, E., & Ridlo, A. (2018). Pengaruh Pencahayaan terhadap Kandungan Pigmen Tetraselmis chuii sebagai Sumber Antioksidan Alami. *Buletin Oseanografi Marina*, *7*(2), 91. https://doi.org/10.14710/buloma.v7i2.19995
17. He W.; Li, L.-X.; Liao, Q.-J.; Liu, C.-L.; Chen, X.-L. (2011). *Epigallocatechin gallate inhibits HBV DNA synthesis in a viral replication-inducible cell line. World J. Gastroenterol. 17, 1507. [CrossRef] [PubMed]*
18. Imanishi, N.; Tuji, Y.; Katada, Y.; Maruhashi, M.; Konosu, S.; Mantani, N.; Terasawa, K.; Ochiai, H. (2002). *Additional inhibitory effect of tea extract on the growth of influenza A and B*

viruses in MDCK cells. J. Microbiol. Immunol. 46, 491–494. [CrossRef]

19. Jassim, S.A.A. & Naji MA. (2003). Novel antiviral agents: a medicinal plant perspective. J. Appl. Microbiol. 95(3): 412–427.
20. Jaswir, I., Noviendri, D., Hasrini, R. F., & Octavianti, F. (2011). Carotenoids: Sources, medicinal properties and their application in food and nutraceutical industry. *Journal of Medicinal Plant Research*, *5*(33), 7119–7131. https://doi.org/10.5897/JMPRx11.011
21. Jo, S., Kim, H., Kim, S., & Kim, M. S. (2019). *Characteristics of flavonoids as potent MERS - CoV 3C - like protease inhibitors*. *July*, 2023–2030. https://doi.org/10.1111/cbdd.13604
22. Jo, S., Kim, S., Shin, D. H., & Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *35*(1), 145–151. https://doi.org/10.1080/14756366.2019.1690480
23. Lalani, S. & Chit. L. P. (2020). Flavonoids as Antiviral Agents for Enterovirus A71. *Viruses Journal*, *71*(184), 2–34. https://doi.org/doi:10.3390/v12020184
24. Landrum, J.T. (2010). Carotenoids Physical, Chemical, and Biological Fuction and Properties. CRC Press. New York.
25. Lani, R.; Hassandarvish, P.; Chiam, C.W.; Moghaddam, E.; Chu, J.J.H.; Rausalu, K.; Merits, A.; Higgs, S.; Vanlandingham, D.; Bakar, S.A. (2015). *Antiviral activity of silymarin against chikungunya virus*. Sci. 5,11421. [CrossRef]
26. Lewis, J. E., Mcdaniel, H. R., Agronin, M. E., Loewenstein, D. A., Riveros, J., Mestre, R., Martinez, M., Colina, N., Abreu, D., Konefal, J., Woolger, J. M., & Ali, K. H. (2013). The effect of an aloe polymannose multinutrient complex on cognitive and immune functioning in Alzheimer's disease. *Journal of Alzheimer's Disease*, *33*(2), 393–406. https://doi.org/10.3233/JAD-2012-121381
27. Maoka, T. (2020). Carotenoids as natural functional pigments. *Journal of Natural Medicines*, *74*(1), 1–16. https://doi.org/10.1007/s11418-019-01364-x
28. Michell. S. Santos, L. S. Leka, J. D. Ribaya-Mercado. (1997)."Short- and long-term beta-carotene supplementation do not influence T cell-mediated immunity in healthy elderly persons," The American Journal of Clinical Nutrition, vol. 66, no. 4, pp. 917–924.
29. Miki, K.; Nagai, T.; Suzuki, K.; Tsujimura, R.; Koyama, K.; Kinoshita, K.; Furuhata, K.; Yamada, H.; Takahashi, K. (2007), *Anti-influenza virus activity of biflavonoids*. Bioorg. Med. Chem. Lett. 17, 772–775.[CrossRef]
30. Milani, A., Basirnejad, M., Shahbazi, S., & Bolhassani, A. (2017). Carotenoids: biochemistry, pharmacology and treatment. *British Journal of Pharmacology*, *174*(11), 1290–1324. https://doi.org/10.1111/bph.13625
31. Moradi, M., Karimi, A., Shahrani, M., & Hashemi, L. (2019). *Anti-Influenza Virus Activity and Phenolic Content of Pomegranate (Punica granatum L .) Peel Extract and Fractions*. *11*(4), 285–291.
32. Nagai, T.; Moriguchi, R.; Suzuki, Y.; Tomimori, T.; Yamada, H. *Mode of action of the anti-influenza virus activity of plant flavonoid, 5, 7, 40-trihydroxy-8-methoxyflavone, from the roots of Scutellaria baicalensis*. *Antivir. Res.* **1995**, *26*, 11–25. [CrossRef]
33. Ngginak, J., Mangibulude, J. C., & Rondonuwu, F. S. (2017). The Identification of Carotenoids and Testing of Carotenoid Antioxidants from Sand Lobster (Panulirus homarus) Egg Extract. *ILMU KELAUTAN: Indonesian Journal of Marine Sciences*.https://doi.org/10.14710/ik.ijms.22.3.155-160
34. Ngginak, J., Rafael, A., Amalo, D., Titin, S., & Sandra, C. L. (2020). *Analisis Kandungan Senyawa β- Karoten pada Buah Enau (Arenga piñata) dari Desa Baumata*. Jambura edubiosfer jurnal. Vol.No. *2*(1), pp: 1–7
35. Ngginak, J., Apu, M. T., & Sampe, R. (2021). Analisis Kandungan Saponin pada Ekstrak Serat matang Buah Lontar (Borassus flabellifer Linn). *BIOEDUKASI (Jurnal Pendidikan Biologi)*, *12*(2), 221. https://doi.org/10.24127/bioedukasi.v12i2.4451
36. Novoveská, L., Ross, M. E., Stanley, M. S., Pradelles, R., Wasiolek, V., & Sassi, J. F. (2019). Microalgal carotenoids: A review of production, current markets, regulations, and future direction. *Marine Drugs*, *17*(11), 1–21. https://doi.org/10.3390/md17110640
37. Olson, J. A. (1989). Biological actions of carotenoids. *Journal of Nutrition*, *119*(1), 94–95. https://doi.org/10.1093/jn/119.1.94
38. Padamani, E., Ngginak, J., Lema, A. T. (2021). *Analisis Kandungan Polifenol pada Ekstrak Tunas Bambu Betung (Dendrocalamus asper).* Jurnal Bioma. Vol.No. 52–65.https://doi.org/10.32528/bioma.v5i1.3688
39. Panche, A. N., Diwan, A. D., & Chandra, S. R. (2016). Flavonoids: An overview. *Journal of Nutritional Science*, *5*. https://doi.org/10.1017/jns.2016.41
40. Papuc, C., Goran, G. V., Predescu, C. N., Nicorescu, V., & Stefan, G. (2017). Plant Polyphenols as Antioxidant and Antibacterial Agents for Shelf-Life Extension of Meat and Meat Products: Classification, Structures, Sources, and Action Mechanisms. *Comprehensive Reviews in Food Science and Food Safety*, *16*(6), 1243–1268. https://doi.org/10.1111/1541-4337.12298
41. Pesang, M. D., Ngginak, J., Gasper, A., Kase, O., Kelautan, I., Perikanan, F., Kristen, U., Wacana, A., & Timur, N. T. (2020). *Komposisi Pigmen*

pada Ulva sp ., Padina australis dan Hypnea sp . dari Pantai Tablolong Provinsi Nusa Tenggara Timur. *23*(2), 225–233.

42. Prianti, S. (2014). Review; *Potential production of carotenoids from Neurospora*. Jurnal Nusantara bioscience. Vol.No. 6.1. pp: 63-68 ritton, G., S.L. Jansen and H. Pfander. (2008). Carotenoids. Volume 4. Natural Functions. Basel, Switzerland

43. Qaddir, I.; Rasool, N.; Hussain, W.; Mahmood, S. (2017). *Computer-aided analysis of phytochemicals as potential dengue virus inhibitors based on molecular docking, ADMET and DFT studies*. J. Vector Borne Dis. 54, 255.
44. Rao, A. V., & Rao, L. G. (2007). Carotenoids and human health. *Pharmacological Research*, *55*(3), 207–216. https://doi.org/10.1016/j.phrs.2007.01.012
45. Saini, R. K., Nile, S. H., & Park, S. W. (2015). Carotenoids from fruits and vegetables: Chemistry, analysis, occurrence, bioavailability and biological activities. *Food Research International*, *76*(August), 735–750. https://doi.org/10.1016/j.foodres.2015.07.047
46. Salvioli, S., Sikora, E., Cooper, E. L., & Franceschi, C. (2007). Curcumin in cell death processes: A challenge for CAM of age-related pathologies. *Evidence-Based Complementary and Alternative Medicine*, *4*(2), 181–190. https://doi.org/10.1093/ecam/nem043
47. Santoyo S., Jaime L., Plaza M., Herrero M., Rodriguez-Meizoso I., Ibanez E., Reglero G. (2012). Antiviral compounds obtained from microalgae commonly used as carotenoid sources. Journal of Applied Phycology 24:731–741. Springer Science+Business Media B.V. Spain.
48. Sayuna, S., Ngginak, J., & Nitsae, M. (2020). Effect of Variations in Sugar Addition to the Quality of Bamboo Shoot Syrup (Dendrocalamus asper). *Bioedukasi*, *XVIII*(1), 41. https://doi.org/10.19184/bioedu.v18i1.15445
49. Schwarz, S.; Sauter, D.; Wang, K.; Zhang, R.; Sun, B.; Karioti, A.; Bilia, A.R.; Efferth, T.; Schwarz, W. (2014). Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. *Planta Med. 80*, 177–182. [CrossRef
50. Seko, H. M., Sabuna. Ch. A. Ngginak, J. (2021). JBIO : JURNAL BIOSAINS (The Journal of Biosciences). *Ekstrak Etanol Daun Ajeran sebagai Antibakteri Terhadap Staphylococcus Aureus*, *7*(1), 1–9. https://doi.org/https://doi.org/ 10.241 14/jbio.v7i1.22671
51. Sharma S, Chopra K, Kulkarni SK, Agrewala JN. (2007). Resveratrol and curcumin suppress immune response through CD28/CTLA-4 and CD80 co-stimulatory pathway. Clin Exp Immunol ;147(1):155–63
52. Srivastava, R. M., Singh, S., Dubey, S. K., Misra, K., & Khar, A. (2011). Immunomodulatory and therapeutic activity of curcumin. *International Immunopharmacology*, *11*(3), 331–341. https://doi.org/10.1016/j.intimp.2010.08.014
53. Toti, E., Oliver Chen, C. Y., Palmery, M., Valencia, D. V., & Peluso, I. (2018). Non-provitamin A and provitamin A carotenoids as immunomodulators: Recommended dietary allowance, therapeutic index, or personalized nutrition? *Oxidative Medicine and Cellular Longevity*, *2018*. https://doi.org/10.1155/2018/4637861
54. Ucci, M., Di Tomo, P., Tritschler, F., Cordone, V. G. P., Lanuti, P., Bologna, G., Di Silvestre, S., Di Pietro, N., Pipino, C., Mandatori, D., Formoso, G., & Pandolfi, A. (2019). Anti-inflammatory role of carotenoids in endothelial cells derived from umbilical cord of women affected by gestational diabetes mellitus. *Oxidative Medicine and Cellular Longevity*, *2019*. https://doi.org/10.1155/2019/8184656
55. Varalakshmi, Ch., Ali, A. Mubarak., Paradhasaradhi, B. V. V., Srivastava, R. M., Singh, S., Khar, A. (2008). Immunomodulatory effects of curcumin: In-vivo. International Immunopharmacology.8, 688–700. India.
56. Vilchez. C, Forján. E, Cuaresma. M, Bédmar. F, Garbayo. I and Vega. J. M. (2011). *Marine Carotenoids: Biological Functions and Commercial Applications*. Journal Marine Drugs. Vol 9. Hal : 319- 333.
57. Wagner, E. K., Hewlett, M. J., Bloom, D. C. & Camerini, D. (2007). Basic Virology, Wiley
58. Zeb A., Mehmood S. (2004). Carotenoids Contents From Various Sources And Their Potensial Health Applications. Journal Of Nutrition 3 (3): 199-204. Pakistan.
59. Zhang, L., & Liu, Y. (2020). *Potential interventions for novel coronavirus in China: A systematic* review. Journal of Medical Virology, *92*(5), 479–490. https://doi.org/10.1002/jmv.25707

ISSN 2406-8233

BIOLEARNING JOURNAL

ISSN: 2406-8233; EISSN; 2406-8241 Volume 10 No. 2. Juli 2023

Table 2 . Types of flavonoids and their ability to inhibit viral infections (Lalani & Chit (2020)

Flavonoid	Picornavirus	Model	Stage of Virus Inhibition	Suggested Mechanism
3-Methylquercetin	Poliovirus	In vitro	Late replication	Blocked of genomic RNA synthesis
				Reduction in viral protein and RNA synthesis
3-Methylkaempferol	Poliovirus-1	In vitro	Replication	Inhibition of positive-strand of viral RNA
5,30 -Dihydroxy-3,6,7,8,40 -pentamethoxyflavone and 5-hydroxy-3,6,7,30 ,40 -pentamethoxyflavone	Poliovirus-1	In vitro	Replication	Postulated to be inhibition of cellular processes (apoptosis and downstream signaling pathways)
5,7,40 -Trihydroxy-30 -methoxyflavone	Rhinovirus (HRV)	In silico	Entry	Inhibition by binding to human rhinovirus
6-Chloro-40 -oxazolinylflavanone	Poliovirus-2	In vitro	Replication	N/R
	HRV-1B	In vitro	Replication	N/R
7-O-galloyltricetifavan and 7,40 -di-Ogalloyltricetifavan	Coxsackievirus B3 (CV-B3)	In vitro	N/R	N/R
Chrysosplenol C	Poliovirus	In vitro	Replication	N/R
Desmanthin-1	Coxsackieviruses A16 (CV-A16)	In vitro	Replication	N/R
Dihydroquercetin	Coxsackievirus B4 (CV-B4)	In vivo	Indirect: Immune-mediated infection control	Reduction in viral immune mediators (ROS-mediated signaling and oxidative stress
Epigallocatechin-3-Gallate	Poliovirus-1	In vitro	Virucidal effect (irreversible)	N/R
Eupafolin	CV-A16	In vitro	Attachment	Reduction in IL-6 and RANTES and inactivation of downstream signaling pathways (ERK1/2, c-Jun, and STAT3)
Kaempferol-3-O-[2",6"-di-O-Z-p-coumaroyl]- β-d-glucopyranoside and derivatives	CV-B3	In vitro	Replication	N/R
	HRV-1B	In vitro	Replication	N/R
Luteolin	CV-A16	In vitro	Replication	Inhibition of viral RNA synthesis

| Flavonoid | Picornavirus | Model | Stage of Virus Inhibition | Suggested Mechanism |

ISSN 2406-8233

BIOLEARNING JOURNAL
ISSN: 2406-8233; EISSN; 2406-8241 Volume 10 No. 2. Juli 2023

	Poliovirus	In vitro	Replication	N/R
Myricitrin	CV-A16	In vitro	Replication	N/R
Pachypodol (RO 09-0179)	CV	In vitro	Early replication	Interference with viral replications between the uncoating and RNA synthesis stage
	Poliovirus	In vitro	Late replication	Blocked the synthesis of positive-strand RNA
	HRV	In vitro	Early replication	Interference with viral replications between the uncoating and RNA synthesis stage
Prunin	Enteroviruses A and B	In vitro and in vivo	Translation and replication	Inhibition of IRES activity and protein synthesis
Quercetin	Encephalomyocarditis virus (EMCV)	In vivo	Indirect: Immune-mediated infection control	Activation of macrophages
	Mengo virus	In vivo	Indirect: Immune-mediated infection control	Activation of macrophages
	HRV	In vitro	Transcription and translation	Reduction in endocytosis of virus and phosphorylation of Akt (effector of phosphoinositol 3-kinase). Repression of interferon and interleukin-8 response resulted in lower viral RNA and capsid protein production.
	HRV	In vivo	Indirect: Immune mediated infection control	Suppression of viral immune mediators
RO 09-0298	CV-B1	In vivo	N/R	N/R
Sakuranetin	HRV-3	In vitro	Replication	Antioxidant activity through inhibition of viral adsorption