Update on Pharmacological Aspects of Carotenoids: Molecules of Pharmaceutical Promise

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

I have acknowledged all main sources of help

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Approval

The thesis titled "Update on Pharmacological Aspects of Carotenoids: Molecules of Pharmaceutical Promise" submitted by Marium Akther Labanna (18146002) has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human and animal trial.

Dedication

Dedicated to my parents and my project supervisor Sania Ashrafi mam

Acknowledgement

First and foremost, I would want to express my gratitude to Almighty for his endless gifts, which have been given to me in an effort to provide me with the strength and determination to complete this project job.

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List of Acronyms

FDAFood and drug administration

CAMComplementary and alternative medicine

ROSReactive oxygen species

IPPIsopentenyl pyrophosphate

MVAMevalonic acid

MEPMethylerythritol phosphate

IDIIsopentenyl diphosphate isomerase

DMAPPDimethylallyl pyrophosphate

CECapillary electrophoresis

PCNA Proliferating cell nuclear antigen

PPAR-γ Peroxisome proliferator- activated receptor-γ

ATM Ataxia telangiectasia mutated

TRAIL Tumor necrosis factor apoptosis including ligand

VEGF Vascular endothelial growth factor

BDNF Brain derived neurotropic factor

LPSLipopolysaccharide

LDL Low density lipoprotein

GJC Gap junctional communication

TRTriodothyronine receptor

RARRatinoic acid receptor

PGD Prostaglandin D

CREB Camp reponse element binding protein

HIF1 Hypoxia inducible factor

BAL Bronchoalveolar lavage

MMP 9 Matrix metalloproteinase

TNF Tumor necrosis factor

TC Total cholesterol

TG triglycerides

OGD oxygen glucose deprivation

MBC Minimum bactericidal concentration

HSV Herpes simplex virus

HBVHepatitiesB virus

HCVHepatitiesC virus

CHIKV Chikungunya virus

DENV Dengue virus

EGFR Epidermal growth factor receptor

ALT Alanine transaminase

AST Aspartate transaminase

AP Activator protein

IGF Insulin like growth factor

MCF 7 Michigan cancer foundation

AMD Age related macular degeneration

CVD Cardiovascular disease

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Abstract

Carotenoids are photosynthetic light-absorbing pigments found in plants. They are well known for their pharmacological activities in different ailments. Plants, fungi, algae, and different microorganisms are the natural sources of carotenoids. These molecules are most commonly known for their antioxidant properties. Rather than that, they are found to be effective against some other severe diseases. The present study aims to accumulate these molecules as a new therapeutic agent, as they have substantial efficacy to prevent and minimize the symptoms of many conditions like cancer, diabetes, inflammation, atherosclerosis, depression, neurodegenerative diseases such as Alzheimer, cerebral ischemia and many more. Yet more research and analysis are needed to make these pharmacologically active compounds usable to mankind. In this study we have reviewed the sources, biosynthesis, separation and pharmacological activities of different naturally occurring carotenoids.

Keywords: Carotenoids, Pigments, Biosynthesis, Mechanism, Separation, Identification, Natural sources, Clinical trial, Biochemical activity.

1 Introduction

Herbal goods, often known as phytomedicines, are treatments that are derived from plants and are solely meant for internal usage in the repair or prohibition of diseases. It's referred to as an ayurvedic nutritional ingredient. A large number of prescriptions, including over-the-counter medications, are also made from plant components, but only pure compounds are used, and the FDA regulates them. Supplements derived from plants may be made up of complete Plants or plant components are included. Herbal supplements are available in many forms, including chopped, dried, capsules, powdered, and liquid, and may be applied in a number of different ways. They're taken as tablets, powders, or tinctures. Tea gels and creams are brewed as lotions and applied to the skin as lotions, gels, or creams.(*Anatomy of the Urinary System | Johns Hopkins Medicine*, n.d.) Drugs from natural sources also have a low risk of side effects. Herbal medicine is mostly used to treat severe and long-term ailments. It is less expensive than traditional medication, and it's less challenging to get than prescribed medications. It helps to keep metabolism and hormones under control, encourages the body's process of healing and strengthens the body's immune system, and it is low-cost and has fewer side effects.(*Benefits of Herbal Medicine | Global Events |USA| Europe | Middle East | Asia Pacific*, n.d.). Traditional medicine includes plant, animal, and mineral-based medications, spiritual treatments, and physical methods, which are applied independently or in aggregation, to treat illnesses as well as to improve wellness. Complementary medicine is used in combination with conventional medical care, but it is not a stand-alone therapy. Acupuncture is one example of how it might be used to help with the side effects of cancer treatment. In lieu of traditional medicine, alternative medicine is used. One example is the adoption of a specific diet in place of cancer drugs prescribed by an oncologist. Complementary and alternative medicine refers to medicinal manufacture, methods which are not considered to be portion of grade medical treatment (CAM). This might be used to manage treatment-related adverse effects, including nausea, pain, and tiredness. They may be able to unwind and forget about their concerns about treatment and the tension that comes with it. Some complementary and alternative treatments have undergone extensive testing and have been shown to be generally safe and effective. In CAM treatment, botanicals and nutritional goods, including herbal and dietary supplements, as well as vitamins, are employed.(*Complementary and Alternative Medicine (CAM) - National Cancer Institute*,

n.d.). Carotenoids are natural substances that give vegetables and fruit their vibrant red, yellow, and orange colors. Carotenoids are obtained from fruits and vegetables in high concentrations. Carotenoids are found in a variety of fruits and vegetables. The health of the plant is dependent on these pigments. To give a better understanding of carotenoids, they are phytonutrients that may be found in the cells of a broad range of creatures, such as bacteria plants, and algae. The Linus Pauling Institute at Oregon State University is dedicated to the work of Linus Pauling. They contribute to photosynthesis by aiding plants in the absorption of sunlight. Moreover, they work as antioxidants by inhibiting the formation of free radicals, which are single oxygen atoms that interact with other molecules to cause cell damage. In addition, carotenoids have been found to possess antioxidant effects in the human body. According to the Physicians Committee for Responsible Medicine, they possess carotenoid, which has strong cancer-fighting capabilities. Moreover, carotenoids such as lutein and zeaxanthin are processed by the body into vitamin A, which is necessary for healthy eyesight as well as development and growth that is seen as common. Carotenoids have anti-inflammatory and immune system enhancing properties, and they have been linked with the prevention of cardiovascular disease in several studies. Furthermore, carotenoids have been shown to have health-promoting characteristics. Carotenoids have a large number of biological functions, including anti-inflammatory, anticancer, antibacterial, immunomodulatory, antidiabetic, and neuroprotective properties. Carotenoids lower oxidative stress in the host body via a variety of ways, including acting as scavengers of free radicals and upregulating antioxidant enzyme synthesis.(*What Are Carotenoids? | Live Science*, n.d.). Carotenoids are categorized into two types: xanthophylls, which include oxygen, and carotenes, which are pure hydrocarbons with no oxygen. Oregon State University's Micronutrient Information Center is part of the Linus Pauling Institute. Xanthophylls are readily identified by their yellow color and are numerous in leaves. Xanthophylls are also responsible for the color of vegetables and fruits, including papaya, squash, and peaches. As well as their role in vision, they contribute to the protection of the retina from blue and ultraviolet radiation, which may trigger the formation of radical ions in the tissue. Carotenoids with no oxygen atoms are known as carotenes. The proportion of the light reflected by them is red and orange in color.Carotenoids are the pigments that give carrots, sweet potatoes, and melons their color. Carotenes function as an auxiliary pigment by converting light energy into chlorophyll. This may subsequently be utilized to store energy in the form of glucose. Carotenes are present in modest

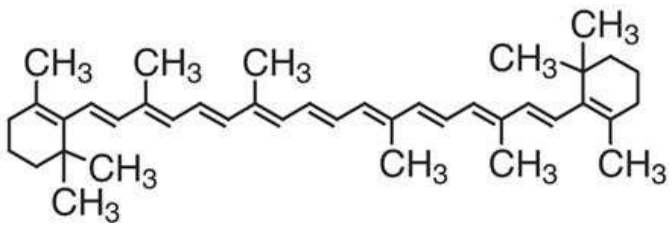
concentrations in almost all vegetables and fruits. Despite the fact that animals cannot produce carotenoids, they play an important function in metabolism and serve as precursors to a variety of chemicals. https://biologydictionary.net/carotenoids/ The primary goal of this study is to consolidate the latest knowledge on carotenoids' bioactive qualities and to emphasize the possible health advantages for humans. Furthermore, this review promotes the use of carotenoids in medicinal settings.(Young & Lowe, 2018).

2 Chemistry & Chemical Formula of Carotenoids

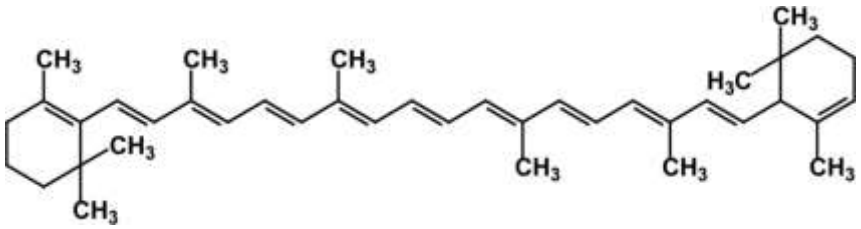
2.1 Chemistry of carotenoids

Carotenoids are a group of hues present in plants that act as light-absorbing pigments during photosynthetic processes. Carotenoids have a lot of conjugation because they can swap single and double bonds with pi electrons that aren't in the same place as the bonds. Carotenoids are a type of tetraterpene. They contain 40 carbon atoms in total and are composed of four terpene units containing ten carbon atoms each. Carotenoids are polyene hydrocarbon chains with rings at the ends that may or may not be physically connected to extra oxygen atoms (Namitha& Negi, 2010).

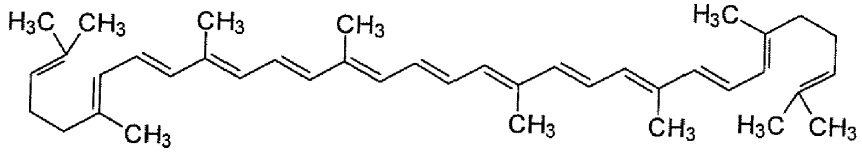
The carotenoid's overall structure is made up of a polyene chain of molecules. with 9-11 double bonds and perhaps ending in a ring structure. As chemical properties, all carotenoids have a polyisoprenoid structure with a large chain of conjugated double bonds, and around the core double bond, there is almost equal symmetry. Carotenoids are synthesized by cyclizing the end groups and adding oxygen functions to the basic structure, which results in their various colors and antioxidant properties.(Rao & Rao, 2007).



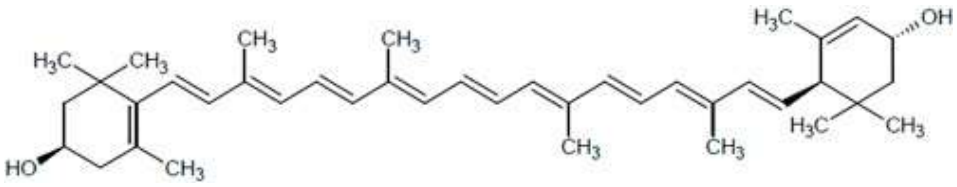
β-carotene



α-carotene



Lycopene



Lutein

Figure 1: Structures of Some Naturally Occurring Carotenoids

Carotenoids are classified into two major groups:

1. carotene (beta-carotene, Lycopene), a cyclic or linear molecule composed entirely of hydrogen and carbon.

2. Oxy carotenoids (xanthophylls, lutein) are trivalent compounds of hydrogen, carbon, and oxygen.

The polyene chains of carotenoids contain up to 15 conjugated double bonds, which contribute to their photochemical and distinct absorption spectra properties(Britton, 1995). Their responsibilities might include reducing superoxide anion and absorbing potentially hazardous free radicals and reactive oxygen species (ROS) among other things They may engage in a variety of antioxidant defense systems as a result of these characteristics. The majority of carotenoids exist in a linear or all-trans form(Krinsky, 1989).The isomerization of one or more double bonds from trans to cis may be facilitated by exposure to light or heat in certain cases.

2.2 Chemical Formula of Carotenoids

Absorption spectra in the ultraviolet and visible ranges, chromatographic studies, and chemical tests to determine the kind position in Xanthophylls, as well as the number of functional groups may all be used to reliably identify carotenoids with known structure.

Antioxidant capabilities of carotenoids may be connected to their structural features, which include

1. There is a plurality of densely packed energy between the excited state and the ground state, which enables them to release excited state energy through minor collisional interactions with the solvent.

2. They have a limited ability to sensitize additional molecules when stimulated.

3. By enabling delocalization and stability of the excited state, resonance states may be generated.

4. Active oxygen attack on carotenoids may occur in a variety of locations. Each double bond in their;the polyene chain may be either trans or cis. in nature, they are mostly or fully trans. Because cis isomers have a lower thermal stability than trans isomers, they are less frequent,due to the increased steric barrier caused by a cis double bond between adjacent the presence of hydrogen atoms and methyl groups(Dutta et al., 2005).

3 Distribution of Carotenoids in Nature

3.1 Photosynthetic Tissue

Carotenoids are pigments found in photosynthetic tissues that are found in the grana of the chloroplast. They all belong to the same main category of pigments. There are four of these: fl-carotene (Formula 2), lutein (3,3'-dihydroxy-ct-carotene), violaxanthin (5,6,5',6'-diepoxyzeaxanthin), and neoxanthin (Formula 6). Alpha carotene (Formula 3), beta cryptoxanthin (3-hydroxy-fl-carotene), zeaxanthin, and antheraxanthin are also detected in trace levels. In green tissues, the partially saturated precursors are detected at a concentration 1/200 that of beta carotene. Although the xanthophylls are present in their natural state, during autumn senescene, when the chloroplasts disintegrate, the xanthophylls released into the cytoplasm are commonly esterified before being oxidatively destroyed(Wiss& Gloor, 1970).From a nutritional standpoint, it is the amount of beta carotene, the most potent naturally occurring precursor to vitamin A(Wiss& Gloor, 1970).

3.2 Non-Photosynthetic Tissue

3.2.1 Reproductive tissues

Carotenoids accumulate in chromoplasts in carotenogenic flowers, , which seem to emerge from chloroplasts in the same way as carotenogenic fruit, seems to be the same.Carotenoids are also found in carotenogenic fruit. Carotenoids are produced by three types of flowers:

(i) those that contain highly oxidized pigments such as auroxanthin, a furanoid oxide.

(ii) hydrocarbons, for example, lycopene

(iii) Carotenoids that are very unique to a certain species, such as the retro carotenoids chscholtzxanthin found in *Eschscholtziacali Jornica*

On ripening, when a green unripe fruit has chloroplasts progressively convert to chromoplasts, and as the photosynthetic system disintegrates, enzymes are either synthesized or depressed, and carotenoid synthesis, typically of unique colors, is greatly increased. Tomatoes and red peppers are two common examples.

3.2.2 Roots

The carrot is the most prominent carotenogenic root, with fl-carotene being the predominant pigment in commercial types and xanthophylls accounting for only about 5% of the total pigments present(Wiss& Gloor, 1970).

Additionally, certain sweet potatoes contain substantial levels of beta-carotene,

3.3 Algae

Numerous carotenoids were discovered in various algal divisions or classes.

Allene (C=C=C): It is a very uncommon structural element that can be found in nature; fucoxanthin can be found in brown algae and diatoms, 19′-acyloxyfucoxanthin can be found in Dinophyta, Haptophytes and peridinin can only be found in dinoflagellates, and 9′-cis neoxanthin can be found in algae and plants.

Acetylene (C_2H_2):acetylenic carotenoids are found only in algae,crocodextrin, and monadoxanthin,alloxanthin are found in the Cryptophyta, while diadinoxanthin and diatoxanthin are found in the Haptophyta,Heterokontophyta,EuglenophytaandDinophyta, families.

Acetylated carotenoids (-O-CO-CH3): peridinin, Fucoxanthin, and dinoxanthin are all pigments found mostly in algae, particularly in the Haptophyta,DinophytaandHeterokontophyta, families. These carotenoids are only found in a small number of algal divisions and classes, which makes them very rare(Takaichi, 2011).

Table 1: Distribution of Carotenoids in Plants (Nagarajan et al., 2017)

Parts of Plant	Scientific Name	Common Name	Carotenoid
Root	*Daucus carota* L.	Carrot	α-carotene, β-carotene
	Ipomoea batatas	Sweet potato	β-carotene
	Dioscorea spp.	Yam	α-carotene, β-carotene, lutein, zeaxanthin

	Allium fistulosum L.	Onion	β-carotene, lutein
Leaf	*Spinacia oleracea*	Spinach	Lutein, β-carotene
	Lactuca sativa	Lettuce	Lutein, β-carotene
	Rosmarinus officinalis	Rosemary	β-carotene
Flower	*Crocus sativus* L.	Saffron	Lycopene, α-carotene, β-carotene, zeaxanthin
	Rosa sempervirens L.	Rose	β-carotene
	Tagetes ereectal	Marigold	Lutein
Fruit	*Solanum lycopersicum*	Tomato	Lycopene, β-carotene
	Curcurbitamoschata	Pumpkin	α-carotene, β-carotene, lutein, lycopene, β-cryptoxanthin, zeaxanthin
	Citrullus lanatus	Watermelon	Lycopene, β-carotene
	Carica papaya	Papaya	Lycopene
	Malpighia emarginata	Acerola	β-carotene, lutein, β-cryptoxanthin
	Actinida sp.	Kiwi	Lutein, β-carotene
	Capsicum annuum	Red capsicum/paprika	β-carotene, zeaxanthin, β-cryptoxanthin
	Citrus sinensis	Orange	α-carotene, β-carotene, lutein, β-cryptoxanthin,
	Pyrus communis L.	Pear	β-carotene, lutein, β-cryptoxanthin,
	Prunus persica L.	Peach	α-carotene, β-carotene, lutein, β-cryptoxanthin
	Malus domestica	Apple	α-carotene, β-carotene, lutein, β-cryptoxanthin
	Prunus avium	Cherry	α-carotene, β-carotene, lutein, β-cryptoxanthin

Seed/Grain	*Oryza sativa*	Black rice	α-carotene, β-carotene
	Zea mays	Corn	α-carotene, β-carotene, lutein, β-cryptoxanthin, zeaxanthin

Figure 2: Natural Sources of Carotenoids

4 Biosynthesis of Carotenoids

Carotenoids and other isoprenoids are synthesized from isopentenyl pyrophosphate, a 5-carbon (5C) molecule (IPP). Two sources of IPP exist inside plants.

1. The cytosolic mevalonic acid (MVA) pathway is responsible for the production of mevalonic acid.

2. the methylerythritol 4-phosphate (MEP) pathway, which is generated from plastids(Lichtenthaler et al., 1997)

The enzyme IPP isomerase (IDI) catalyzes the conversion of IPP to its allylic isomer, dimethylallyl pyrophosphate (DMAPP), which serves as the first, activated substrate for the production of sesquiterpenes (C15) and triterpenes (C30), such as sterols, prior to the initiation of chain extension.(Laule et al. 2003; Hsieh and Goodman 2005) When DMAPP is combined with a molecule of IPP, geranyl pyrophosphate is formed.

Themethylerythritol 4-phosphate pathway is restricted to chloroplasts and is the principal component of plant isoprenoids. It is also the most efficient route. (Clairmont et al., 1996).The IPP and DMAPP enzymes employed in The MEP pathway is responsible for the production of carotenoid biosynthesis in plants.Enzymes belonging to the carotenoid cleavage dioxygenase (CCD) family may cleave carotenoids into apocarotenoids along the route. Apocarotenoids are a family of terpenoids that comprise several significant volatile chemicals such as geranyl acetone, ionone, pseudoionone, and 3-hydroxy-io-none(Auldridge et al., 2006; Simkin et al., 2004).

5 Separation and Identification of Carotenoids from Natural Sources

5.1 Methods of Separation

In Methods of separationBio compounds need to be separated based on their physical and chemical qualities Listed below are some of the most frequently utilized separation procedures in biomaterial mixture separation that are often encountered.(Butnariu, 2016):

• Distillation

• The formation of crystals.

• Dialysis

• Electrophoresis

• Thin-layer chromatography and column chromatography

5.2 Overview of General Separation Methods

5.2.1 Distillation

When a volatile ingredient is separated from a nonvolatile material, the process is known as distillation. Water reaches boiling point at 100 degrees Celsius, while ethyl alcohol reaches boiling point at 78 degrees Celsius. It is necessary to mix water and steam in a flask which is then heated until steam is produced.It will evaporate (turn into gas) and flow through the still's column before entering the condenser, where it will be transformed back to liquid form. Plant carotenoids may be extracted in the same way as animal carotenoids can be separated, via the use of distillation..(Butnariu, 2016).

5.2.2 Dialysis

In this approach, the differential in biocomponent diffusion through a semipermeable membrane is used to separate and purify the bioactive compounds. The obtaining force behind.The differential in concentration between the two sides of the membrane is what causes dialysis to take place. independent of the method through which the operation is performed. Carotenoids are separated and purified using the molecular distillation process, which is a type of vaporization that occurs at low pressures and low temperatures. It has proven to be particularly useful in the separation and purification of materials with high molecular weight molecules, as well as for those that are thermally sensitive (such as carotenoids), as it helps to reduce losses due to thermal decomposition.(Butnariu, 2016).

5.2.3 Electrophoresis

Using transformation rates in an electric field, capillary electrophoresis (CE) may be used to separate dissolved or suspended compounds from a liquid in which they are dissolved or suspended. The number of positive or negative ions produced by a macromolecule is governed by the composition of the macromolecule, as well as the pH and ionic strength of the surrounding environment, among other factors. In this study, a methacrylate ester-based

monolithic column was utilized to analyze carotenoids (beta-carotene and lycopene) utilizing a methacrylate ester-based methacrylate ester in order to determine their concentrations.(Zou et al., 2013).

5.2.4 Chromatography

When biocomponents are isolated from a mixture using chromatography (a technology established for the separation or analysis of difficult mixtures), the components are separated at the time of elution from the column. During the separation process, the stationary phase is composed of granular adsorbent material contained in a row, and the aqueous layer is comprised of a solution of the mixture to be separated contained in a liquid solution.Carotenoids can be separated from a mixture by using chromatography in a time efficient manner(Butnariu, 2016).

5.3 Separation Methods for Carotenoids

The polarization of the molecule and the chemical bonding are important considerations that govern their hydrophilic character play a role in separating carotenoids from a mixture. Column chromatography with aluminum or another adsorbent is used to separate each phase, utilizing ether, ethyl alcohol: ether, and acetone as eluents. The cleanest fractions for which thin layer chromatography is used to assess purity are 50–100 mL(Butnariu, 2016).

5.4 Identification Methods

Any bio substance may be identified using physical and chemical methods. The following are the techniques for recognizing carotenoids.

5.4.1 UV–Visible spectra

Electronic spectra are spectra derived from the absorption of radiations having wavelengths.(120 to 1000) nm in the ultraviolet, visible, and near infrared wavelength ranges.Changing the energy of valence electrons causes electromagnetic wave absorption in theultraviolet (140–400 nm) and visible (400–800 nm) wavelength ranges. Measurements of carotenoids at wavelengths that correspond to their absorption maxima may be carried out quantitatively when the extinction molar coefficients at those wavelengths are known.(Krasnovsky& Kovalev, 2014).

5.4.2 IR spectra

Carotenoids are comparable to polyenes in structure and optical characteristics because they include -electron-conjugated carbon-chain molecules. Because a given maximum of absorption may be ascribedto a certain degree of resonance transfertypical to certain groups.IR spectroscopy can help solve some structural difficulties for these molecules(Faheem et al., 2012).

5.4.3 Nuclear Magnetic Resonance Spectra

The fact that the energy included are substantial in the commencement of the NMR phenomena are minimal ensures that the examined carotenoic compounds are unaffected by the energy's influence on the carienoidic compounds under research(Butnariu, 2016).

5.4.4 Mass Spectrometry

Mass spectrometry is built on the electron bombardment modification of the studied carotenoids into ions, after which the ions are separated,faster, and produced. It is possible to establish the precise ratio of the molecular mass by calculating the mass of the molecular ion. structures of these bio compounds have been identified based on the information gathered, features that may be linked to functional groups in the (Kopec et al., 2013).

5.4.5 Chemical Methods

Specialized reagents and procedures unique to various functional groups may be used to detect carotenoids. Using a mixture of procedure.The following functional groups may be determined by chemical changes and other implies:(Butnariu, 2016):

Hydroxyl (–OH)	Amide (–CONH2)
Ether (–O–)	Nitrile (–CN)
Carbonyl (C=O)	Nitro (–NO2)
Carboxyl (– COOH)	Nitroso (–N=O)
Ester (–COOR)	Amine (–NH2)
Anhydride (–CO)2O	Azo (– N=N–)

6 Pharmacokinetics Activity

Pharmacokinetics is the branch of pharmacology that studies how medicines get to their target sites and then get eliminated from the body. Individual responses to drugs are determined by the drug's inherent pharmacological qualities at the site of action.The systems that determine the rate at which a drug accumulates in and is eliminated from a body include absorption, distribution, metabolism, and excretion.

6.1 Astaxanthin

Astaxanthin's pharmacokinetic characteristics were dosage dependent and dose independent in rats after intravenous and oral treatment. After oral dosing, The flip-flop concept was followed by the absorption of astaxanthin.The first-pass extraction ratios in the hepatic and gastrointestinal tracts were around 0•490 and 0•901, respectively. Astaxanthin was stable for 4 hours in rat stomach fluids and 24 hours in a variety of buffer solutions ranging in pH from 1 to 13(Choi et al., 2011).

6.2 Crocetin

Crocetin was more quickly absorbed and identified in plasma after a single oral dosage in humans than other carotenoids such as luteinandlycopene(Umigai et al., 2011).Crocetin did not cause any major side effects, and its pharmacokinetics were shown to be dose proportional within the dosage range employed. Due to the fact that the less bound chemical (Crocetin) is often widely dispersed throughout the system, this research concentrated on absorption rather than elimination(Umigai et al., 2011).

6.3 Lutein

After oral administration, a significant quantity of lutein remained in the intestinal mucosa, while only negligible levels were identified in distant organs. Lutein exhibited a limited bioavailability, suggesting that it was not widely distributed to distant organs during that time period. Increased meal consumption was used to try to increase intestinal absorption, which resulted in a shorter time interval between peak concentration (Cmax) and peak AUC (Tmax)(A. M. Ahmad, 2007).

7 Mechanism of Action of Carotenoids

7.1 Antioxidant Activity

It is most probable that carotenoids are engaged in the scavenging of two (ROS), peroxyl radicals and singlet molecular oxygen, among other things, in the body. Furthermore, they are efficient deactivators of thermally stimulated molecules, which are responsible for the generation of radicals and singlet oxygen in the environment.(Stahl & Sies, 2003). It is primarily physical quenching that is responsible for the majority of the interaction between carotenoids and singlet molecular oxygen, which involves direct energy transfer between the two molecules. As a consequence of the transfer of energy from a singlet molecular oxygen to a single molecule, the creation of ground state oxygen and a triplet excited carotene is achieved.Rather than undergoing an additional process of chemical, the carotene is returned to the lower state, squandering its resources by contact with the solution. Among the many carotenoids are xanthophylls and carotenes, which have been shown to be effective quenchers of singlet oxygen whose reaction rates are nearing those of the dispersion control system. beta-Carotene, along with zeaxanthin, cryptoxanthin, and a-carotene, is a very potent quencher of singlet molecular oxygen. Lycopene accounts for up to 30% of the total carotenoid content in humans. Carotenoids are considered to have a critical function in preventing oxidative damage to cellular membranes and lipoproteins. They are produced during the process of lipid peroxidation, and their scavenging disrupts the chemical sequence, ultimately resulting in damage to lipophilic compartments. It has been proposed that unfavorable effects associated with high-dose b-carotene supplementation may be due to bad effects associated with this supplement.(Stahl & Sies, 2003).

7.2 Intercellular Communication

Carotenoids enhance intercellular communication by raisingthe level of gene transcription that codes for the membrane proteins function that seems unrelated to the vitamin A or antioxidant activity of different carotenoids (26) and involves a RAR-independent mechanism(*Carotenoids | Linus Pauling Institute | Oregon State University*, n.d.).

7.3 Immune Response

Additionally, carotenoids may control immune cell activity through modulating a variety of other distinct or related cell activities. These carotenoids (particularly the polar versions) may govern the fluidity of biological membranes by intercalating into the membrane of lipid of the cell, enhancing the mobility of the membrane's polar head groups and hence the region's accessibility. Additionally, carotenoids may modify the metabolic status of these cells, perhaps by inducing heat shock protein,by the enhancement of intercellular transmission and the reduction of arachidonic acid oxidation , all of which are free radical-induced processes(Chew, 1993).

7.4 Anti-cancer Activity

7.4.1 Cell Cycle Arrest

Among the most important traits of cancer cells is an abnormal cell cycle. Carotenoids has been demonstrated to limit tumor cell proliferation by interfering with several stages of the cell cycle.Inhibition of cell cycle progression is the most important processes through which lycopene decrease the risk of cancer. Lycopene expanded the number of cells in the S and G2/M stages in pituitary adenoma cells via inhibiting Skp2(Haddad et al., 2013).

Lycopene has been reported to have an anti-proliferative impact on human colon carcinogenesis cells by inhibiting the formation of cyclin D1, suppressing the phosphorylation of the pRB protein, and increasing the amount of p27KIP in the cells. Cell growth in human hepatoma cells was reduced by up to 50% after treatment with lycopene, and cells were arrested in the G0/G1 and S phases as a result of the therapy.(Palozza et al., 2009).

A study conducted on human pancreatic cancer cells found that crocetin and crocin, which are major carotenoid products discovered in the Saffron plant.Saffron suppressed the growth of the cancer cells by halting the cellular proliferation from progressing through the G1 and G2/M phases.(Bakshi et al., 2010).Additionally, in a xenograft mouse model, it reduced pancreatic cell growth and tumor development. By decreasing PCNA expression and survival, astaxanthin significantly lowers the occurrence of colon adeno carcinoma in mice in an in vitro research(Niranjana et al., 2015).

Fucoxanthin has been discovered to promote cell cycle arrest in hepatocellular carcinoma,neuroblastoma, hepatocellular carcinoma, melanoma, leukemia, colon, and prostate cancer cells.Fucoxanthin reduced neuroblastoma cell growth in the G0 or G1 phase of the cell cycle.In hepatocarcinoma and prostate cancer cells, treatment triggered G1 phase arrest. Fucoxanthin exhibited anti-proliferative activities in lung cancer cells, which were investigated by assessing cell proliferation generated by continuous and discontinuous carotenoid administration(Okuzumi et al., 1990).

7.4.2 Apoptosis

Apoptosis is a kind of planned cell demise; a malfunction in the apoptosis pathway is identified as a significant characteristic of cancer cells. Sensitivity to apoptosis develops in carcinogenesis cells as a result of overexpression of anti-apoptotic proteins or mutations in pro-apoptotic proteins. Carotenoids has been shown to have chemo preventive properties by lowering the occurrence of cancer in humans through apoptosis(Gosslau& Chen, 2004).

Lycopene has been shown to have potent anti-cancer capabilities, including the ability to induce apoptosis.In breast cancer cells, it increased the expression of the proapoptotic protein Bax as well as the cleavage of PARP resulting in the death of the cells (Takeshima et al., 2014).

Following lycopene therapy, a substantial rise in the proportion of apoptotic cells was seen in lung cancer cells. This was accompanied by a significant increase in caspase-3 activation. Beta Carotene controlled apoptosis in breast cancer cells by stimulating PPAR-gamma and increasing the formation of ROS, carboline suppressed lung cancer cell growth and promoted apoptosis. Carbene boosted p53 levels andBcl-2 anti-apoptotic activity was decreased, as was the number of nuclear ataxia telangiectasia-mutated cells (ATM) in gastric cancer cells at a dosage of 100 M(Jang et al., 2009).

Neoxanthin decreased the endurance of human prostate cancer cells by stimulating caspase-3 and PARP(Kotake-Nara, Asai, et al., 2005).

In colon cancer cells, neoxanthin initiated apoptosis through defeat of mitochondrial transmembrane potential and consequent enhanced cytochrome and apoptosis persuading factor (AIF) release(Terasaki et al., 2007).

Violaxanthin ineffective proliferation and triggering early apoptotic changes in breast cancer cells.in addition, violaxanthin-treated cells did not exhibit DNA division or delay apoptotic alterations (Pasquet et al., 2011).

In uveal melanoma cell lines from humans, zeaxanthin caused apoptosis via activating the intrinsic apoptosis signaling system, which resulted in caspase-9 and -8 activation and enhanced cytochrome c release. Fucoxanthin has been shown to induce apoptosis in a variety of cancer cell lines, including, leukemia hepatoma, colon,urinary bladder , andprostate cancer cells. The ROS-mediated Bcl-xL pathway and PARP cleavage also played a role in leukemia cells dying from fucoxantha.

Canthaxanthin induces apoptosis in colon and skin cancer cells in a dose-and time-dependent manner. It madeJNK, p38,and ERK1/2 more phosphorylated in colon cancer cells when it worked.

Fucoxantha triggered apoptosis by lowering the mitochondrial membrane potential and activating caspase-9 and -3, but not by producing ROS.(Kotake-Nara, Terasaki, et al., 2005).

Because of the ROS-induced Bcl-xL and JAK/STAT pathways, fucoxanthin has an antitumor effect. This is mostly because the EGFR is down-regulated.In leukemia, breast, and colon cancer cells, fucoxanthins were discovered to promote apoptosis.

(J. Wang et al., 2012).

Peridinin, a marine-derived carotenoid, triggered apoptosis by activating caspase-8 and -9, which are engaged in the apoptosis receptor and mitochondria-signaling pathways, respectively.

(Sugawara et al., 2007).

Siphonoxanthin has already been demonstrated to promote autophagy in human leukemia cells by blocking the autophagy mediated by the Tumor necrosis factor apoptosis inducing ligand (TRAIL) in these cells.

7.4.3 Inhibition of Metastasis

Lycopene decreased the metastatic characteristics (, invasion, adhesionand migration) of human hepatic adenocarcinoma (SK-Hep1) cells by inhibiting the gelatinolytic activity of the MMP-2 and MMP 9 enzymes. Lycopene substantially inhibited the migration of sk-hep1 cells in migration experiments(C. S. Huang et al., 2008).

The discovery of innovative anti-metastatic medications with minimal toxicity and great effectiveness is one of the most effective areas of contemporary anti-cancer research. At a dose of 5 M, all carotenoids exhibited the greatest inhibitory impact on AH109A cells. Further investigations using astaxanthin shown that they reduced the invasive activity of AH109a cells that was enhanced by ROS. Lycopene inhibited cell invading and movement in highly invasive hepatocarcinoma cells by high expression development of the metastatic suppressor gene Nm23-H1.. When used at a concentration of 5 M, lycopene significantly reduced cell migration and invasion by 91 and 63 percent, specifically.

In SK-Hep1 cells, lycopene and its product, apo-8′-lycopenal, were examined. The findings indicated that they efficiently lowered VEGF, PCNA, and MMP-9 protein expressions while increasing the anti-metastatic gene, Nm 23-H1.

hexamine is a sugar compound discovered in tumor cells that has been linked to cancer. that aids in the manufacture of sialic acid, which enhances tumor cell spreading ability.A recent research found that -carotene efficiently inhibits human hepatocarcinoma cell invasion, migration, and adhesion. Astaxanthin prevented tumor invasion in colon carcinogenesis by lowering extracellular matrix enzyme synthesis(Nagendraprabhu& Sudhandiran, 2011).

Fucoxanthin inhibited cell invasion factors such as MMP-9, CD44 (a cell surface glycoprotein), and CXR4 in metastatic B16F-10 cells (a CXC chemokine receptor).

7.5 Antidiabetic Activity

Beta carotene, which the body converts to a near relative of vitamin A, it may help to decrease the risk of type 2 diabetes, However, gamma tocopherol, which is very common type of vitamin E in the American diet, may contribute to the disease's risk. Furthermore, the fact that beta carotene and gamma tocopherol both increase diabetes risk in different ways implies that the

protein encoded by the SLC30A4 gene may play acrucialrole in the disease13,14. Indeed, the protein is plentiful in the pancreas's insulin-producing islet cells, where it facilitates the transfer of zinc into those cells. This in turn stimulates the release of insulin, whose proper production by the pancreas and effective absorption by muscle, liver, and adipose tissue prevents harmful glucose accumulation in the blood and, in the long term, the establishment of type-2 diabetes.Patients with diabetes worry consequences such as cataracts, diabetic retinopathy, and nephropathy. Indeed, diabetes mellitus is assumed to be connected with a fivefold increased occurrence of cataracts24. Lutein has been demonstrated in one research to have no effect on blood glucose levels but to lower ROS levels in diabetic retinas. Lutein exerted its impact in the retina, at least on part, by reducing diabetes-induced local ROS. Additionally, ROS associated with neural activity have an effect on the production of BDNF. This factor is engaged in the regulation of axonal development, synaptic action , and neuronal survival. Although the amount of BDNF is lowered in the diabetic retina, lutein therapy reverses this decline and protects neuronal cells from apoptosis.According to a research, astaxanthin derived from shrimp waste had a strong hypoglycemic impact when administered orally to diabetic mice induced with alloxan. Oral dose of astaxanthin effectively controlled postprandial hyperglycemia by lowering the postprandial AUC(Sayahi& Shirali, 2017).

7.6 Anti-Inflammatory Activity

The ROS transmission route interacts with the nuclear factor B (Nf-B) signaling pathway in a number of different ways. Inhibition of Nf-B transcription has an influence on the quantity of ROS in the cell, which in turn has an impact on the amount of Nf-B activity. The ROS has the potential to both promote and inhibit Nf-B signaling. Nf-B is a transcription factor that has been shown to be engaged in the activation of inflammatory and immunological processes. According to a generally accepted theory, NOS2 activity suppresses signal transduction in the Nf-B transcription factor pathway. In addition to stimuli that stimulate the generation of NOS2 and NO, COX2 expression may be induced by other factors. A common association between inflammation and iNOS activity is the formation of nitric oxide, which in turn enhances COX2 catalytic activity by forming the peroxinitrite anion. The enzyme COX2 is a NOS2 target. According to a research, lycopene inhibits the LPS-induced pro-inflammatory mediator-inducible nitric oxide pathway in mouse macrophage cells, which is associated with

inflammation. Both beta-carotene and lycopene have been shown to increase the expression of the Hmox1 gene in humans. According to our findings, the strong activation of Hmox1 gene expression by these polyene compounds may be due to the generation of electrophilic intermediates during the oxidation of carotenoid pigments. These intermediates may enhance the efficiency of the electrophile (EpRE)/ARE transcription pathway, as well as activate phase II enzymes and NRF2-targeting enzymes, among other things (superoxide dismutase, glutathione peroxidase, catalase, and HMOX1). The antioxidants beta-carotene and lycopene had strong pro inflammatory effects by inhibiting the expression of the Cox2, Nos2, and Tnfa genes, as well as by up-regulating the production of the Hmox1 gene.(Kawata et al., 2018).

7.7 Anti-hypercholesterolemic Activity

It is becoming more recognized that LDL oxidation is aimportantearly event in the expression of heart disease. Inflammation of the endothelium is triggered by oxidized LDL, and this results in atherosclerosis and vascular thrombosis (heart attack and stroke). Carotenoids may act by inhibiting the production of cholesterol by the enzyme 3-hydroxy-3-methylglutaryl coenzyme a (HMGCoA) reductase (HMGCoA). The results of newly in vitro studies on LDL oxidation revealed that beta-carotene in LDL is oxidized before the polyunsaturated fatty acids in LDL are oxidized, indicating that beta-carotene may have a role in delaying the initiation of LDL oxidation in humans. Carotene combines with peroxyl radicals to produce a carbon-centered carotenyl radical, which, in a manner similar to a lipid free radical, reacts with oxygen to make a carotene peroxyl radical, allowing chain propagation to proceed. Researchers have discovered that carotenoids may reduce in vivo lipid peroxidation processes, demonstrating that their presence in cell membranes is required for them to function as structural stabilizers. Molecules 2012, 17 4760 Lutein was shown to be particularly efficient in inhibiting the oxidation of LDL and restricting the inflammatory response of monocytes in reaction to LDL that had been stuck in the artery wall, according to Dwyer et al. In addition, they discovered that supplementing with lutein decreased plasma lipid hydroperoxides as well as the frequency of aortic lesions in two animal models of coronary artery disease (apoE-null mice and LDL receptor-null mice).(Dwyer et al., 2001).

Additionally, Fuhrman and colleagues revealed that in cholesterol synthesis feeding macrophage cell lines with lycopene lowered the cholesterol synthesis and improved LDL receptors. In vitro

treatment with lycopene resulted in a 73 percent decrease which was bigger than the reduction found with beta carotene(Agarwal et al., 2012).

8 Biochemical Activities of Carotenoids against Different Conditions

8.1 Antioxidant Activity

8.1.1 Lutein/Zeaxanthin

In male Swiss albino mice, a 100 mg dose of lutein/zeaxanthin revealed considerable, moderately antioxidant activity in the presence of zeaxanthin.(Milani et al., 2017).

8.1.2 Zeaxanthin

While zeaxanthin is capable of scavenging both water-and lipid-soluble peroxyl radicals, when their polar groups are exposed to an aqueous environment, they may react with radicals produced in that zone. They also have an impact on the compressive energy and permeability of the membrane, which has an effect on oxygen and other molecule permeabilities.(Krinsky et al., 2003).

8.1.3 β-carotene

β-Carotene has been found to block the rise in the production of the heme oxygenase-1 gene in cells transfected with has been discovered (FEK4) when exposed to ultraviolet A radiation, suggesting an amount of the drug's pro-oxidant activity in this cell type(El-Agamey et al., 2004; Rao & Rao, 2007).

8.1.4 Lycopene

It has been proved to be a substantial antioxidant in mice to reduce ROS produced by smoke inhalation and to modify redox-sensitive cell targets such as, protein kinases, protein tyrosine phosphatases ,transcription factors, and MAPKs.(Kaulmann& Bohn, 2014).

Lycopene has the ability to enhance autophagy in Journal Pre-proof cells. Lycopene was reported to increases the production of autophagy-related genes (Atg14, , P62, Lc3, Atg7 and Beclin) in the adipose tissue of bloated mice(Zhu et al., 2020).

Lycopene prevented ROS overproduction, lipid peroxidation and, increased antioxidant capacity in adipocytes, and lowered NOX subunit gene expression. Additionally, lycopene increased the production of genes encoding antioxidant enzymes such as GSH-Px, SOD, and CAT(Zhu et al., 2020).

8.1.5 Astaxanthin

Astaxanthin acts as an antioxidant by scavenging reactive oxygen speciesand protects brain cells by inhibiting decadent cascades. Ischemia of the retina may result in inflammation and oxidative stress, both of which can result in damage. Ischemia/reperfusion of the retina boosted NF-B production and produced retinal inflammation in the laboratory.(Ishizuka et al., 2013).

8.2 Effect on Intercellular Communication

Intercellular communication may be described as the exchange of information between two cells. It is a subfield of cell biology that also includes the study of cellular organelles and signaling. Three modes of intercellular communication exist. Certain chemical compounds released by certain cells are transferred to distant locations where they function as signals for other cells; the surface molecules of a group of cells communicate with their neighboring cells; and certain specific junctions or next facilitate direct communication between cells.

8.2.1 β-Carotene

Depending on the carotenoid, it increased gap junctional communication (GJC) in murine fibroblasts by more than fivefold. Carotene has been reported to be useful in the diagnosis of various types of cancer.(Kong & Korea, 1994).Carotene and retro hydro beta carotene were the most effective inclines of GJC, demonstrating that the existence of a 6-member ring is required for GJC induction; carotenoids with 5 -member rings had limited action.

8.2.2 Retinoic acid

It stimulates cellular communication, resulting in the differentiation of F9 cells. It has been proposed that mechanism is controlled by the protein connexin , which promotes the production of key particles involved in cellular adhesion.(Eichele, 1997).

8.2.3 Zeaxanthin

Zeaxanthin has been found to protect RGC-5 cells against oxidation by reactive oxygen species (ROS) mediated by H2O2, O2 -, and HO. After 20 minutes of pretreatment with 0.1–100 M zeaxanthin and staurosporine, intracellular radicals were scavenged.Damage produced by H2O2 exposure resulted in a 50%–60% reduction in cell viability. 1 M zeaxanthin reduced this drop greatly and marked injured cells more strongly than normal cells with the dye formazan (WST-8).The vitality and oxidative stress of RGC-5 cell cultures were determined. Serum deprivation for 24 hours decreased cell viability, but pretreatment with 1 mg zeaxanthin enhanced cell oxidative stress considerably (reduced production of reactive oxygen species(Nakajima et al., 2009).

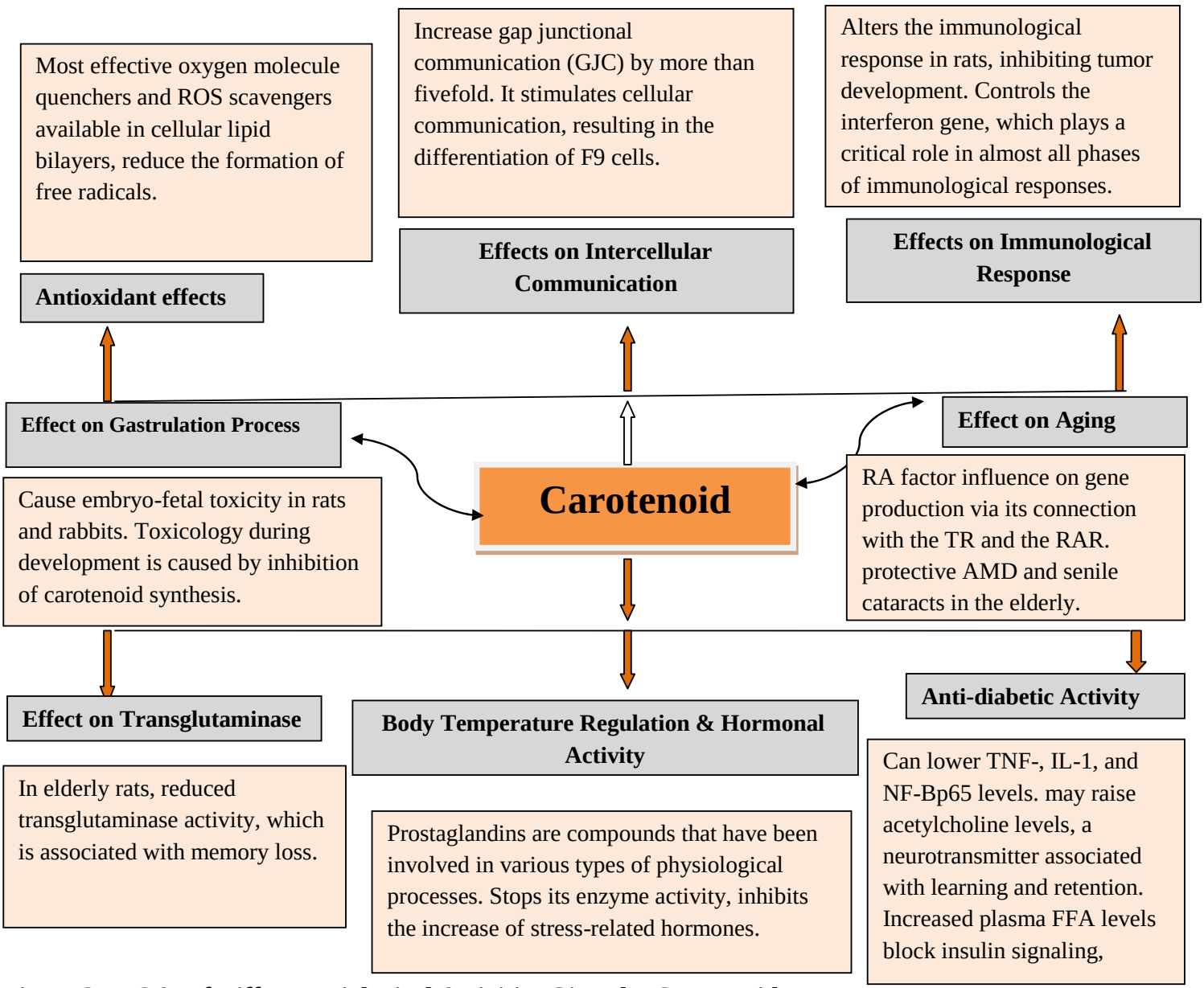


Figure 3: MOAs of Different Biological Activities Given by Carotenoids

8.3 Effect on Immunological Response

8.3.1 β-Carotene

It alters the immunological response in rats, hence inhibiting tumor development. It has been shown that retinoic acid controls the interferon (IFN-) gene, which plays a critical role in almost all phases of immunological and inflammatory responses(Article, 2012).

8.3.2 Astaxanthin

It was shown that the carotenoid astaxanthin, which lacks vitamin A action, boosted the resource of human immunoglobulins (IgA, IgM, and IgG) in mice when they were exposed to T cell-contingent stimuli.(Sasaki et al., 2010).In healthy women, ASTA may decrease a biomarker of DNA damage and boost immunological response. Additionally, significant increases in neutrophil phagocytic and fungicide M of ASTAm capabilities were seen after therapy(MacEdo et al., 2010).

8.3.3 Curcumin

Curcumin may also influence adaptive immunity by increasing T cell proliferation(Varalakshmi et al., 2008).

8.4 Effect on Gastrulation Process

Gastrulation is a very early prodromal phase inwhere a fetus evolves after a one layer of epithelial cells (blastula) to a multilayer and multidimensional structure called as the gastrula.Additionally, it is a formative process that establishes the three germ layers, which are predecessors to all embryonic tissues, and the embryo's axial orientation.

8.4.1 Retinoic acid

In vitro, it plays a critical function in the gastrulation process. Alcohol dehydrogenase class IV was discovered at that time, and it was hypothesized that the adverse effects of alcohol intake on fetal growth could be caused by the inhibition of retinoic acid synthesis, which is catalyzed by alcohol dehydrogenase, leading to the dysfunction of the retinoic acid receptor (necessary for normal development).(Clairmont et al., 1996; Preet et al., 2013).

8.4.2 Lycopene

It has been shown to cause embryo-fetal toxicity or teratogenicity in rats and rabbits at doses of 3000 mg per kg per day in rats and rabbits. In rabbits, 2000 mg/kg per day is administered. toxicology during development(Milani et al., 2017).

8.5 Effect on Aging Process

8.5.1 Retinoic acid

It has also been linked to the progression of the aging process. Rheumatoid factor (RA) has an influence on gene production levels via its connection with the TR and the (RAR) It is noteworthy that when the TR and RAR mRNA levels in the brains of young, adult, and elderly rats were measured, lower values were revealed than previously thought.The levels of TR and RAR mRNA went up because of the supplementation..(Ang et al., 1996; Upadhyaya et al., 2007).

8.5.2 Lutein and Zeaxanthin

It has been suggested that it may be protective against macular degeneration and senile cataracts in the elderly.(Olson & Krinsky, 1995).

8.6 Effect on Transglutaminase Activity

8.6.1 Retinoic acid (vitamin A)

In elderly rats, retinoic acid lowered transglutaminase activity, which was restored after RA therapy. Transglutaminase has been implicated in memory formation.(Ang et al., 1996).

8.7 Effect on Body Temperature Regulation and Hormonal Activity

8.7.1 Retinoic acid (vitamin A) and Retinol

Prostaglandins are compounds that have been involved in various types of physiological processes, most notably the stimulation of endogenous sleep and the control of various central activities (body temperature regulation, luteinizing hormone release), among others. It has recently been demonstrated that prostaglandin D (PGD) synthase binds retinoic acid and retinol. On the other hand, all-trans retinoic acid stops its enzyme activity, but retinol doesn't.(Hall et al., 2011).

8.7.2 β-Carotene

It has been proposed that β-carotene inhibits the increase of stress-related hormones(G van Poppel R A Goldbohm, 1995).

8.8 Effect on Neuron Development

8.8.1 Retinoic acid (vitamin A)

It was hypothesized that retinoids may control the production of PGD and PGD2, and that synthase may act as a transporter of retinoids to the site of action. Thus, it was proposed that PGD synthase is required for the control of neuronal development by regulating the transfer of all-trans or 9-cis-retinoic acid to RXR or RAR in the juvenile nervous system.(Hall et al., 2011).

8.8.2 Crocetin

It has been found to shield neurons from the destructive impacts of 6-hydroxydopamine (6-OHDA) and to be useful in the protection of Parkinson's disease.. (A. S. Ahmad et al., 2005). Crocetin diagnosis specifically lowered the Bcl-2/Bax mRNA ratio in AGS cell lines and significantly increased caspase activity in these cells.

8.8.3 Zeaxanthin

Zeaxanthin has been shown to have neuroprotective properties. Zeaxanthin may also scavenge H2O2, O2, and HO radicals in addition to staurosporineradicals.Pretreatment with 1–100 M zeaxanthin for 20 minutes demonstrated that it scavenged intracellular radicals in a concentration-dependent manner. It may act as an antioxidant in RGC-5 cells to produce its neuroprotective properties.(Nakajima et al., 2009).

8.8.4 Lutein

Lutein has neuroprotective properties. Lutein's neuroprotective properties against the neuronal disruption that occurs in the retina during inflammation. At a dosage of 100 mg/kg body weight, lutein reduced STAT3 activation, ROS buildup, and other STAT3-related processes in C57BL/6 mice. It prevents dopaminergic neurons from MPTP-induced apoptosis and motor dysfunction via reducing mitochondrial damage and oxidative stress. Mitochondrial dysfunction and

apoptosis mediated by the OS have a role in a variety of neurodegenerative illnesses, including Parkinson's disease, Alzheimer's disease, and more. MPTP, Huntington's disease, is the most frequently employed neurotoxin for the development of Parkinson's disease symptoms. Its mechanism of action is to prevent the mitochondrial complex from functioning properly while simultaneously creating an excessive quantity of intracellular ROS.(Nataraj et al., 2016).Thus, lutein protects the nerves from injury by lowering oxidative stress and the quantity of apoptotic cells.(Bolhassani et al., 2014).

8.8.5 Lycopene

Excessive free radical generation may cause damage to nerve cells, neurotransmitters, synapses, and receptors. Lycopene has been shown to reduce MDA, TBARS, and nitric oxide levels in diabetic and fructose-induced insulin resistance rats.(Zhu et al., 2020).

8.8.6 Astaxanthin

It has neuroprotective properties. In vitro, Astaxanthin reduced retinal cell mortality and ROS generation generated by OGD stress in a concentration-dependent pattern in the in vitro investigation.(Imai et al., 2010).

8.9 Effect on Macrophages Development

8.9.1 Canthaxanthin

Canthaxanthin mixed with low-density lipoproteins (LDL) reduced the development of macrophages from human monocytes. However, when canthaxanthin and LDL were given to cellular media concurrently (but without prior mixing), no impact was detected.(Ang et al., 1996).

8.9.2 β-Carotene

When combined with LDL, it reduced the development of macrophages from human monocytes(Ang et al., 1996).

8.10 Anti-tumor Activity

8.10.1 α-Carotene, Fucoxanthin and Halo Cynthia xanthin

Combinations of the carotenoids alpha-carotene, fucoxanthin, and halo Cynthia xanthin showed a greater inhibitory action against human neuroblastoma cell growth.(Susan Taylor Mayne & Taylor, 1996).

α-Carotene showed more antitumorigenic activity in rats forced to develop cancer with glycerol, and it was noted that carotenoid with a ring exhibited greater inhibitory action(Susan Taylor Mayne & Taylor, 1996).

SK-Hep-1 cell line (2.5 M)Cell invasion inhibition demonstrates hepatocarcinoma action. At the same concentration, AC had more antitumor activity than BC.(Milani et al., 2017).

8.10.2 Lycopene

Lycopene is a potential carotenoid for the protection and diagnosis of human malignancies due to its various tumor-inhibitory properties(Bhuvaneswari et al., 2005).

8.10.3 Crocin

A study demonstrated the efficacy of crocin in the protection of moderately severe anxiety by raising the amount of caffeine consumed and the levels of CREB, BDNF, and VEGF in the hippocampus.(Ghasemi et al., 2015).

8.10.4 β-Carotene

Hypoxia-inducible factor 1 (HIF1), a well-characterized tumor metastasis regulator, also inhibited the migration and invasion of malignant neuroblastoma cells.(MacEdo et al., 2010).

It acts as a chemopreventive agent in the BE(2)C cell line and male BALB/c nu/nu mice, inhibiting neuroblastoma attack and transfer via hypoxia inducible factor1 alpha (HIF-1)(Milani et al., 2017).

Cancers of the skin 3.3mg of beta-carotene, 100mg of canthaxanthin, and 168mg of phytoene reduced the number of skin tumors in female SKH/hr mice. 198. Mathews Roth(Milani et al., 2017).

8.10.5 Curcumin

Incubation with 25 M curcumin could trigger apoptosis in tumor cells but not in initial cultures or non-transformed cells when exposed to comparable circumstances (e.g., 24 h incubation with 25 M curcumin).(Varalakshmi et al., 2008). Male Swiss ablino mice with a regimen of 1% inhibition of skin tumor growth(Milani et al., 2017).

It has shown action against neck and head cancer in UM-SCC14A, CAL27, UM-SCC1, CCL23, cell lines as well as female athymic nude mice.(Milani et al., 2017)

8.10.6 Curcumin analogs

Curcumin analogs inhibit endothelial cell migration, inhibit AP-1 transcription, and have antiangiogenic action in human fibrosarcoma cells. BAECs, JB6P+, HT-1080, cell lines, and HUVECs(Milani et al., 2017).

8.10.7 Crocetin

It reduced RNA/DNA/production in separated nuclei and the efficiency of pure RNA polymerase II in A-549 (lung adenocarcinoma), VA-13 (SV-40 transformed fetal lung fibroblast), and HeLa cell lines in a dosage pattern according to the results of the study.(Milani et al., 2017).

Corcetin was shown to have antitumor action (in vitro). Crocetin inhibits RNA, DNA, and protein synthesis in three human malignant cells: A549 (lung adenocarcinoma), HeLa (cervical epitheloid carcinoma), and VA13 (SV-40 altered fetal lung fibroblast) dose-dependently, but has no impact on colony formation. Three hours of incubation resulted in a dose-dependent reduction of protein synthesis and nucleic acid.

Additionally, it inhibited DNA and RNA production in isolated nuclei. Crocetin administration resulted in a considerable reduction in nucleic acid synthesis in these cells. Crocetin exposure

resulted in a significantly lower degree of inhibitory effects on macromolecular synthesis in HELa cells.(Xi et al., 2007).

8.10.8 Lycopene

Aids in the reduction of ovarian edema and DNA damage. Lycopene therapy (55 mg/kg) produced by STZ decreased ovarian edema and DNA damage in diabetic rats. It decreased inflammation of the myocardium, deterioration of the heart, and cardiac disorganization in a furan-induced cardiotoxicity paradigm in diabetic rats. It inhibited apoptosis and autophagy in cells by inhibiting ROS production and activating p38MAPK.(Zhu et al., 2020).

8.10.9 Terpenoid (Perillyl alcohol)

It inhibited the growth of lung tumors. Intraperitoneal injection of perillyl alcohol 75 mg/kg three times per week effectively reduced the growth of lung tumors. Perillyl alcohol was also discovered to have strong cytotoxic activity against the human malignant cell lines HCT-116, SF-295, and OVCAR-8. Perillyl alcohol inhibited tumor development in mice by 35.3 percent and 45.4 percent, respectively, at doses of 100 and 200 mg/kg/day.There was no evidence of a toxicologically significant influence on liver and renal parameters.(Zeng et al., 2017).

8.10.10 Canthaxanthin

Both in vivo and in vitro, antitumor efficacy has been shown. Canthaxanthin has been shown to be anticancer in vivo and in vitro. It also worked on cell lines from mice with melanoma, fibrosarcoma, and human squamous carcinoma. outcome was a rise in the number of TUNEL-positive nuclei.(D. S. Huang et al., 1992).

8.11 Anti-Mutagenesis Activity

8.11.1 Mexican green peppers (*Capsicum annuum*)

When nitroarenes were tested, they inhibited mutagenicity by more than 90%. Pepper carotenoids were more effective antimutagens than pure carotene, revealing that additional carotenoids included in pepper extracts (e.g., lutein, zeaxanthin) acted synergistically with

carotene. Additionally, it was claimed that the antimutagenic effect might be due to their ability to prevent harmful chemicals from entering the cell or their antioxidant activity.(Murakami et al., 1996).

8.11.2 Lutein

The antimutagenicity of carotenoids extracted from Aztec marigold (Tagetes erecta) was determined. While lutein had the most antimutagenic action in marigold extracts, similar to the finding made for pepper extracts, the combination of carotenoids in the marigold extract exhibited the greatest antimutagenic activity. Additionally, an intracellular combination was formed by lutein and 1-nitropyrene (genetic mutation). that reduced 1-nitropyrene's bioavailability and hence its mutagenicity(Mitra et al., 2021).

8.12 Anti-Apoptotic Activity

8.12.1 α-Carotene

At the same dosage, the anti-apoptotic effects of alpha-carotene were greater than those of alpha carotene (J. Chen et al., 2013).

8.12.2 Lycopene

A powerful singlet oxygen quenching agent found in tomatoes has shown various biological benefits, such as antioxidant, anti-inflammatory, cardio protective, anti-carcinogenic, and anti-mutagenic activities. (Bhuvaneswari et al., 2005).

8.12.3 Crocetin

It was also useful in treating traumatic brain damage by suppressing apoptosis early in the damage and promoting vascular proliferation duringthe initial phase of a traumatic brain injury(Bie et al., 2011).Crocetin also shows action against brain damage. Dosing adult Sprague–Dawley (SD) rats cut down on BCL-2 protein production, stopped apoptosis, and helped treat traumatic brain injury.(Milani et al., 2017).

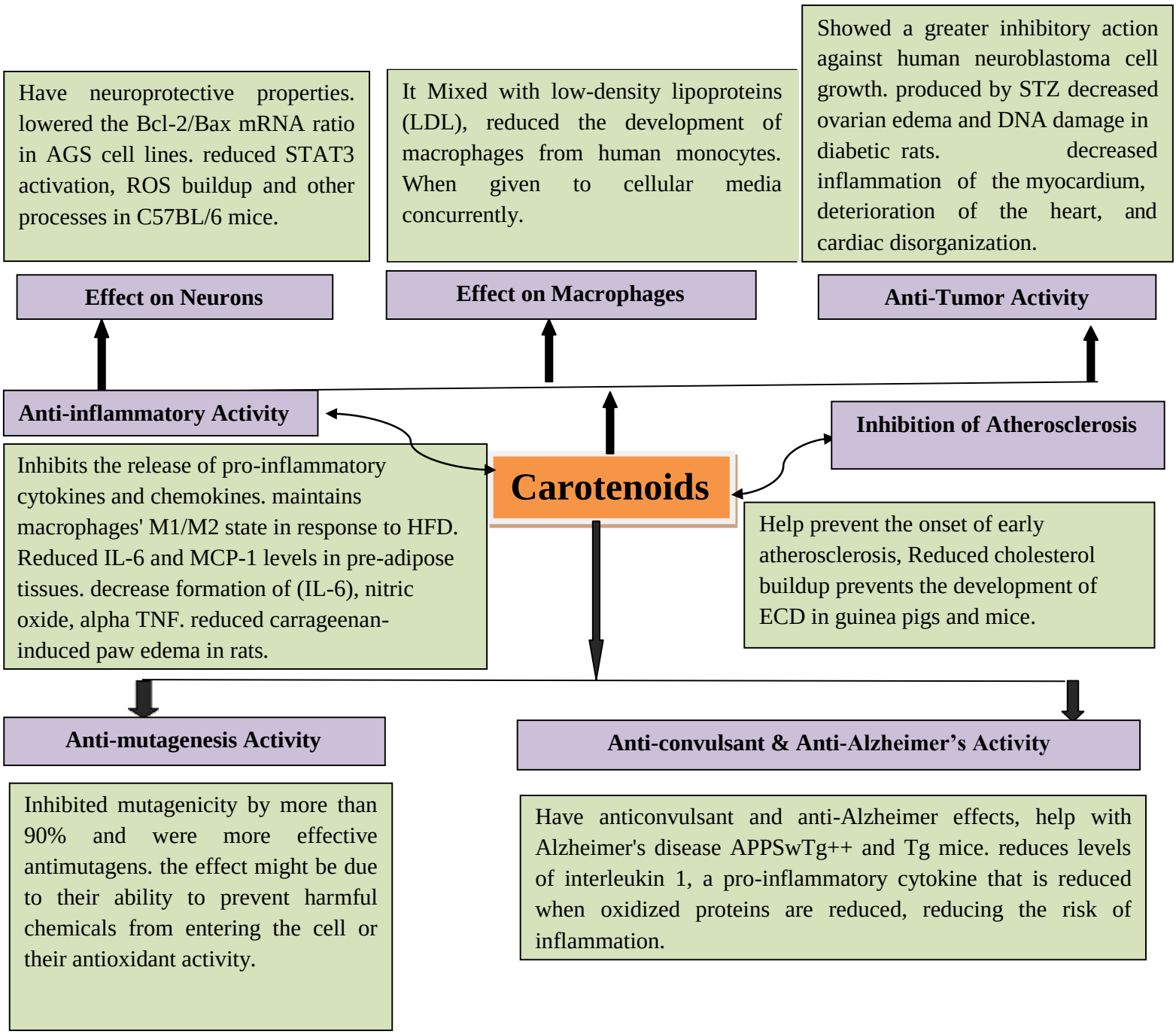


Figure 4: MOAs of Different Biological Activities Given by Carotenoids

8.12.4 Lutein

Dietary lutein inhibited the development of breast tumors and the production of the Bcl-2 gene, which inhibits apoptosis while increasing mRNA production of proapoptotic genes (e.g., Bax and p53), as well as the BaxBcl-2 ratio in tumors.(Krinsky, 2004).By inhibiting apoptosis, they protected the retina from ischemic and hypoxic injury.(Li, Fung, et al., 2012).

8.13 Anti-inflammatory Activity

8.13.1 Lycopene

Lycopene's anti-inflammatory effect was also deemed an important factor in restraining the establishment and advancement of carcinogenesis. Additionally, lycopene acted as an inhibitor of cell invasion, angiogenesis, and metastasis.By inhibiting the Th2 cytokine response, lycopene supplementation lowers allergy inflammation systemically and particularly in the lungs.

Lycopene administration significantly reduced the infiltration of inflamed leukocytes (eosinophils, neutrophils, macrophages, and lymphocytes) into bronchoalveolar lavage (BAL) fluid and was shown to be related to inhibition of the Th2 transcription factor, the cytokine IL-4, GATA-3, and the activity of eosinophil peroxidase in the BAL fluid. and matrix metalloproteinase-9.(Hazlewood et al., 2011).

Additionally, by suppressing the NF-B signaling pathway, lycopene reduced inflammation and apoptosis (e.g., caspase-3, -8, and -9 expression) in postmyocardial infarction remodeling. IL-2, IL-10, IFN-a, TNF-bIL-1, and IL-1Ra are all made and released by human peripheral blood mononuclear cells, but IL-6 and IL-1Ra aren't affected by this drug at all.

Thus, lycopene has been shown to promote inflammatory reactions (Bessler et al., 2008). Lycopene's anti-inflammatory actions in RAW 264.7 macrophages were connected with a reduction in macrophage passage induced by LPS.(Marcotorchino et al., 2012).

Lycopene inhibits the release of pro-inflammatory cytokines and chemokines and maintains macrophages' M1/M2 state in response to HFD. Lycopene pretreatment reduced IL-6 and MCP-1 levels in pre-adipose tissues in response to macrophage inducer or TNF-(54, 55).Similarly,

lycopene reversed the upregulation of M1 marker genes (CD11C and NOS2) and the downregulation of M2 marker genes (CD209A and ARG1) in the epididymal white journal. Obese mice with pre-proof adipose tissue (eWAT)(Gouranton et al., 2011).

8.13.2 Curcumin

Inhibition of MMP-9 (Matrix metalloproteinase) and IL-6 enzyme activity in an astrocyte cell line (U373-MG) in vitro utilizing an LPS-induced inflammatory paradigm. It may generate an anti-inflammatory response in an inflammatory neuronal environment, resulting in CNS healing(Milani et al., 2017).

8.13.3 Lutein and β-cryptoxanthin

It may inhibit the expression of pro-inflammatory factors in rheumatoid arthritis and osteoarthritis.Lutein's anti-inflammatory properties protected the retina against ischemic and hypoxic damage(Li, Fung, et al., 2012).

8.13.4 Lutein/Zeaxanthin

Female SKH-1 mice fed 0.4 percent lutein and 0.04 percent zeaxanthin showed no signs of stress.Inhibition of UV-induced rebound hyperproliferation and reduction of acute inflammation.(Milani et al., 2017).

Lutein Effects on Sore Curing and Cell Proliferation. It inhibited cell proliferation and significantly reduced breast cancer cell passage and attack in a dosage pattern.(Krinsky et al., 2003). Another study looked into how lutenin and oligodeoxynucleotides (ODNs) could work together to help N-nitrosodimethylamine-induced fibrosis.

8.13.5 Terpenoid (Paeoniflorin)

It has shown anti-inflammatory properties in vitro. The majority of monoterpenes have been shown to decrease the formation of interleukin-6 (IL-6), nitric oxide, and tumor necrosis factor alpha (TNF-). Additionally, it is significantly correlated with the dosage. JEUD-38 was separated from the Inula flower(Brinker et al., 2007; J. H. Kim et al., 2017).

8.13.6 Astaxanthin

Astaxanthin has been suggested to have pro-inflammatory properties in a choroidal neovascularization model. Increased oxidative stress activates PARP, which promotes the protein kinase C signaling pathway and increases NF-B. NO, which is produced in response to inflammation, combines with ROS to generate the powerful oxidant peroxynitrite, which results in increased oxidative stress.(Li, Fu, et al., 2012).

8.13.7 Bixin

Tested in male Wistar rats utilizing carrageenan-incited paw edema and myeloperoxidase (MPO) activity, Bixin's anti-inflammatory efficacy was tested in male Wistar rats. Bixin therapy reduced carrageenan-induced paw edema in rats. Bixin has an anti-inflammatory impact, lowering the body's development of anti-inflammatory cytokines (PGs). This is owing to the fact that it acts as an agonist for PPAR alpha and gamma. Bixin has been demonstrated to have an anti-inflammatory impact, lowering the body's production of pro-inflammatory cytokines (PGs)(Takahashi et al., 2009)

8.13.8 Retinoic acid (Vitamin A)

It has been shown that anti-inflammatory action when infected or immunized, Vitamin A and retinoid receptor deficiencies have been associated with decreased T cell responses during infection and immunization.(Hall et al., 2011).There seems to be a lot of influence on the future of T cell immunity from the way RA signals are sent through RARa and RARg. Additionally, Western diets are increasingly being linked to an increase in the incidence of inflammatory illnesses such as allergies and inflammatory bowel disease. (Garrett and colleagues, 2010). Zymosan treatment was shown to make non-mucosal DCs make more RALDH, which helped a model of an autoimmune disease(Hall et al., 2011).

8.13.9 Monoterpene ((–)-Linalool)

In vivo, linalyl acetate exhibited anti-inflammatory and anti-edematous activity. They may contribute significantly to the anti-inflammatory effect of oils containing them. Its ability to

reduce edema in rats using a carrageenan-induced paw edema paradigm is remarkable. This shows that they may have a crucial role in the anti-inflammatory effects of the oils in which they are present.(Koziol et al., 2014).

8.14 Anticonvulsant and Anti-Alzheimer's Activity

8.14.1 Saffron

In animal and human studies, carotenoids found in saffron essence have been shown to have anticonvulsant and anti-alzheimer effects. Depending on how much saffron extract and its components were used, dopaminergic and glutamate levels in the CNS were raised by them.

8.14.2 Curcumin

It has been shown to help with Alzheimer's disease APPSwTg+ and Tg mice. Interleukin-1, a pro-inflammatory cytokine, is reduced when oxidized proteins are reduced. (Milani et al., 2017).

8.15 Inhibition of Atherosclerosis

8.15.1 Lutein/Zeaxanthin

In vivo, female apoE-null mice had 0.2 percent (w/w) atherosclerosis.Lutein/Zeaxanthin Increased lutein intake in the diet may help prevent the onset of early atherosclerosis. In addition, male guinea pigs were fed 0.1 g/100 g of food in vivo. Reduced cholesterol buildup prevents the development of early atherosclerosis.

8.16 Antidepressant Activity

8.16.1 Crocin

In vivo, an anti-depressant-like effect Adult male Wistar Albino rats given 25 and 50 mg/kg crocin demonstrate an anti-depressant-like action in the hippocampus by boosting BDNF, CREB, and VGF levels.(Ghasemi et al., 2015).

8.16.2 Xanthophyll

It has antinociceptive and antidepressant properties (in vivo). Xanthophylls LT, ZX, and LZ modulate ROS and monoamine levels in the brain, as well as protein and mRNA expression and ROS in the spinal cord, to perform their antinociceptive and antidepressant roles. Chronic constriction injury (CCI) was done on animals sedated with ketamine-xylazine (80–20 mg/kg, intraperitoneally). CCI animals had much higher levels of pain, anxiety, and sadness than sham animals.(Bennett & Xie, 1988).

8.16.3 Bixin

Bixin's anti-nociceptive impact is mediated by peripheral and central mechanisms. The capacity of Bixin to inhibit cyclooxygenase (COX) and diminish neutrophil migration (the lowering of MPO activity) was studied in Swiss albino mice. Bixin's possible ability to reduce pain was tested after an acute heat shock of 50 °C. A hot plate device was used to do this.The bare area test was used to assess the impact of interventions on natural locomotor action(Berkenkopf& Weichman, 1988; Meotti et al., 2006; Ribeiro et al., 2000).

8.16.4 Monoterpene

It has a psychopharmacological impact on the central nervous system in vivo. The monoterpene, epoxy-carvone EC was studied in animal models, and it was discovered that it had a psychopharmacological impact on the CNS. The following behavioral changes in mice after 30 and 60 minutes of treatment with EC at dosages of 200 or 300 mg/kg demonstrated a depressant effect on the CNS: decreased spontaneous activity, palpebral ptosis, ataxia, and drowsiness. This could be because the EC has an inhibitory effect on the CNS or because muscle relaxants work in the outside world.(De Sousa et al., 2007).

8.17 Anti-Diabetic Activity

8.17.1 Lycopene

Lycopene aids in the production of insulin in vivo. Oral treatment of a lycopene oil solution restored redox equilibrium in STZ-induced diabetic mice by reducing MDA levels and

enhancing SOD and GSH-Px activity in pancreatic tissue. In diabetic rats and fructose-induced insulin resistance rats, lycopene can lower TNF-, IL-1, and NF-Bp65 levels. It may raise acetylcholine levels, a neurotransmitter associated with learning and retention, by reducing AchE activity in the cerebral cortex and hippocampus.(Heinrich, 2008; Sandikci et al., 2017).

In Swiss albino mice, Sprague-Dawley (SD) rats, HFD-fed New Zealand white rabbits, and C57BL/6J mice, lycopene reduced blood TC, TG, and LDL.Furthermore, lycopene increased fat metabolism and insulin resistance in these mice, preventing weight gain.(Yin et al., 2014).

In males aged 40-80, lycopene intake may lead to a reduction in subcutaneous andvisceral fat mass, and waist circumferences(Kuhad et al., 2008).

8.17.2 Cryptoxanthin

Serum Components in STZ-Diabetic Rats After Cryptoxanthin Administration Animals' body weight reduced dramatically 7 or 14 days following the STZ injection. In rats given STZ, serum glucose and lipid levels were significantly raised, showing that the drug causes a diabetic condition. Normal rats were given cryptoxanthin, which had no influence on blood calcium or inorganic phosphorus levels.(Uchiyama & Yamaguchi, 2005).

8.17.3 Terpenoid (Stevioside (SVS))

A diterpenoid has a hypoglycemic effect. In research, it was discovered that SVS may help rats with hyperglycemia. Its antihyperglycemic impact might be attributed to the production of GRG, liver phosphorylation, mitochondrial ATP, and suppressor of nicotinamide adenine dinucleotide oxidase activity, all of which result in blood sugar reduction.(Yang et al., 2020).

8.17.4 Crocetin

Crocetin protected fructose-fed rats from developing insulin resistance, as shown by a higher HOMA score. High levels of leptin may indicate the body's resistance to the hormone's effects(Duncan et al., 1995).Insulin resistance is now well understood to be caused by adipose tissue. Increased plasma FFA levels block insulin signaling, which is a key inductor of both peripheral and hepatic insulin resistance(Arner, 2003; Bays et al., 2004). In fructose-fed rats,

administration of a TNF-a converting enzyme inhibitor was shown to improve insulin sensitivity(Oda et al., 2004).

8.18 Antimicrobial Activity

8.18.1 Curcumin

It has an anti-malaria action. Male Swiss mice who were given 100 mg/kg of curcumin had malaria treatment, a reduction in blood parasitemia of 80–90%, and a long life expectancy that was much better than before.(Reddy et al., 2005)

Curcumin exhibits action against Helicobacter pylori in C57BL/6 mice at a dosage of 50 g/ml. Curcumin acts as a development vanquisher for Indian Helicobacter pylori strains and heals the total damage produced by Helicobacter pylori.(Milani et al., 2017)

8.18.2 Lutein

Lutein is a kind of carotene found in the blood of malaria sufferers (Vishwanathan et al., 2014).In vitro investigations revealed that lutein had antiplasmodial action at a dosage of 7.10.20 g(J. E. Kim et al., 2012; Li, Fung, et al., 2012).

8.18.3 Monocyclic Monoterpenes (Eugenol)

Eugenol inhibited 30 Helicobacter pylori strains in vitro, resulting in a considerable reduction in their survival(W. Wang et al., 2012).MRSA and MSSA Staphylococcus aureus were also susceptible. Candida albicans pathogenicity in the mouth is significantly linked to immune system dysfunction(Friedman et al., 2002).The effectiveness of these two drugs in the diagnosis of oral candidiasis was tested using an immune suppressed rat model.(Chami et al., 2005).

8.18.4 Acyclic Monoterpenes

(–)-Linalool

Linalool exhibits antimicrobial activity against Gram-positive and Gram-negative microorganisms (Bacillus subtilis and Staphylococcus aureus).(Bacillus subtilis and Staphylococcus aureus) (Porphylomonasgingivalis, Prevotella intermedia, Fusobacterium

nucleatum). The breakdown of the fat membrane structure in these bacteria is the mechanism of action. It interferes with the fundamental mechanics of microbial metabolism, causing them to die(Biosynthesis & Cytokininsi, 1983).

Citral

When tested in the laboratory, it was found to have antiviral activity against HSV-1.This agent's infectivity was reduced by more than 96 percent.(Trombetta et al., 2005).

8.19 Effect on Cardiovascular System

8.19.1 Lutein

It is a powerful antioxidant. Its effects on the cardiovascular system (in the flesh) Despite contradictory relationships between lutein and blood pressure, insulin sensitivity, obesity, and blood lipids, lutein may support atherosclerosis and inflammatory markers.

(Ochiai et al., 2007).Patients with coronary artery disease benefit from lutein's anti-inflammatory properties, which can help to reduce the severity of their symptoms(P. Chen et al., 2016).

8.19.2 Tanshinone IIA (TS)

TS may help toAtherosclerosis, cardiac injury, and hypertrophy are all considerations to keep in mind. In atherosclerosis, TS prevents the oxidation of reduced lipoprotein and the production of pro-inflammatory proteins, as well as stabilizes atherosclerotic plaque.(Yang et al., 2020).

8.19.3 Thymol

It exhibited cardiovascular action.It's a monoterpene with phenolic properties.In isolated ventricular myocytes from dogs, thymol caused cardiac arrhythmias. Inhibition of K+ and Ca2+ currents was responsible for these effects. Peixoto-Neves et al. exhibited endothelium-independent relaxation in isolated rat aorta(Periago et al., 2001).

8.19.4 Carvacrol

Carvacrol lowered BP and heart beat in rats and stoppedL-NAME-induced hypertension(Aydin et al., 2007).This effect was linked to its impact on the TRPV3 channel. In cardiomyocytes

separated from canine and human ventricles, it was also able to suppress L-type Ca2+ currents(Earley et al., 2010).

It promotes cardiovascular function in anesthetized rats and the effects of carvacrol on cardiovascular function in vivo. They discovered that it caused hypotension and prevented hypertension caused by nitro-L-arginine methyl ester. This vasodilating effect was self-contained to endothelial nitric oxide release, but it did include a transduction mechanism involving calcium hypersensitivity and calcium discharge from the sarcoplasmic reticulum modulation in themechanism responsive. They discovered no adrenergic receptors or voltage-dependent vascular L-type calcium channels in isolated rat aortas.

(Aydin et al., 2007).

8.19.5 (1,8-cineole)(eucalyptol)

Both conscious and sedated rats had considerably lower blood pressure after receiving intravenous eucalyptol. Cardiovascular effects in vitro and in vivo utilizing a mixed strategy. According to the scientists, the hypotensive impact was most likely caused by a decrease in peripheral vascular resistance(Paper, 2000; Pinto et al., 2009).

8.19.6 Menthol

It is an astringent,Human cutaneous capillaries may dilate dramatically when exposed to menthol. This seems to include muscarinic receptor activation and/or nitric oxide generation. Menthol was also able to suppress L-type Ca2+ currents in rabbit myocytes derived from the aortic valve(Baylie et al., 2010).

8.19.7 α-Terpineol

The medication exhibited a hypotensive impact in rats at a dosage of 5 mg/kg given intravenously, according to the researchers. A lowering in peripheral vascular resistance might have generated the hypotensive effects(Magalhães et al., 2008).

8.19.8 Linalool

Linalool's hypotension-causing action in anesthetized rats with normal blood pressure has been studied, and it was discovered that this monoterpene caused hypotension and tachycardia.This might indicate a decrease in peripheral vascular resistance.(Santos et al., 2011).

8.19.9 Citronellol

Citronellol is a monoterpene present in several plants that has been applied in traditional drug to treat hypertension(Abegaz et al., 1983).In addition, isolated rings were isolated from the superior mesenteric artery from rats to undergo tests in vitro to produce vasorelaxation.(Bastos et al., 2010).

8.19.10 Sobrerol and limonene

It's the main ingredient in a lot of citrus oils. The impacts of limonene and sobrerol on monocrotaline-induced pulmonary hypertension and right ventricular hypertrophy in rats were studied. Both monoterpenes inhibited the rise in pulmonary arterial medial thickness.(Sun, 2007).

8.19.11 Cymene and Pinene

Anesthetized rats demonstrated hypotension and bradycardia after receiving these pinene and p-cymene compounds intravenously. This impact was most likely caused by vasomotor center inhibition, which resulted in a reduction in compassionate blood circulation to the peripheral arteries and the heart.(Santos et al., 2011).

8.19.12 Myrtenal, Myrtenol and Perillyl Alcohol

Monoterpenes had hypotensive effects on rats when given at concentrations of 1 and 5 mg/kg intravenously. Myrtenal, myrtenol, and perillyl alcohol might be used to prevent or cure cardiovascular disorders(Santos et al., 2011).

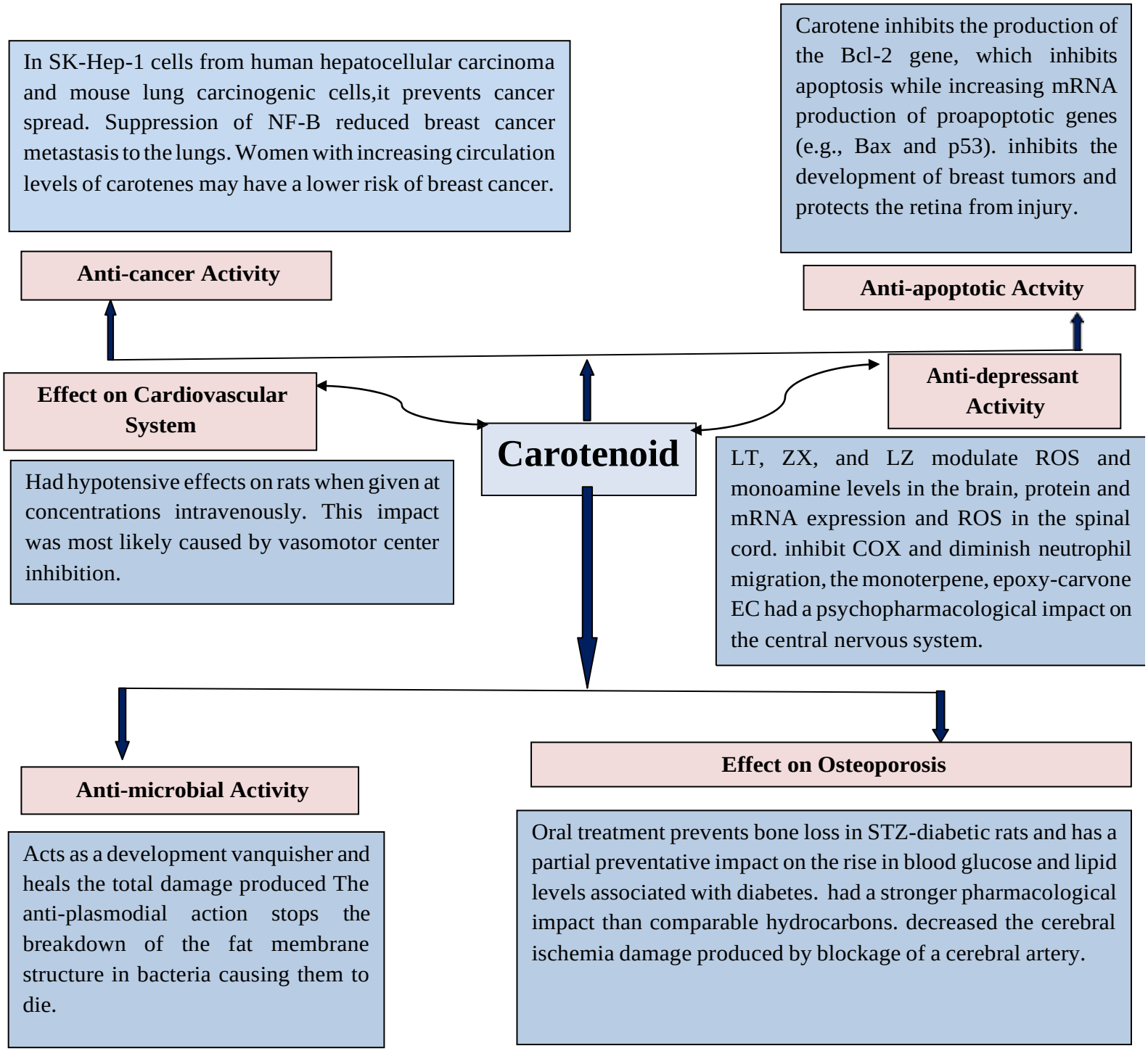


Figure 5: MOAs of Different Biological Activities Given by Carotenoids

8.20 Effects on Osteoporosis

8.20.1 Lutein

Lutein affects both the production of osteoblasts and the degradation of osteoclasts. In mice, the effects of lutein on osteoclastogenesis, bone formation, and femoral bone mass were studied. The effect of macular lutingin on bone density augmentation in young people was studied by Bovier and Hammond.(Eichele, 1997; MacEdo et al., 2010).

8.20.2 Cryptoxanthin

The Effects of beta-Cryptoxanthin on Bone Components in STZ-Diabetic Rats (in vitro)In vitro, oral treatment of beta-cryptoxanthin prevents bone loss in STZ-diabetic rats and has a partial preventative impact on the rise in blood glucose and lipid levels associated with diabetes. In these rats, alkaline phosphatase activity, calcium content, and DNA content in the femoral-diaphyseal (cortical bone) and metaphyseal (trabecular bone) tissues were all considerably lower.(Uchiyama & Yamaguchi, 2005).

8.20.3 α (+)-pinene and β(–)-pinene

The cardiovascular effects of alpha (+)-pinene and beta (–)-pinene have also been studied in non-anesthetized normotensive rats. In rats, these terpenes had hypotensive effects, and terpene alcohols had a stronger pharmacological impact than comparable hydrocarbons. (+)-cis-verbenol decreased the cerebral ischemia damage produced by blockage of a cerebral artery followed by 24-hour reperfusion.(Koziol et al., 2014).

8.21 Anti-Cancer Properties

8.21.1 β-carotene

It is a kind of carotene that is found in WiDr, LS174, and COLO 320 HSR cells that were the most responsive to beta-carotene therapy among several human adenocarcinoma colon cancer cells. After 24 hours of therapy, beta-carotene supplementation boosted apoptotic p53 and

lowered anti-apoptotic BCL-2 in a human gastric cancer cell line (AGS cells).(Niranjana et al., 2015).

Beta-carotene also has anti-colon cancer action (in vitro) in the COLO 320 HSR, WiDr, and LS174 cell lines. In the G2/M phase of the cell cycle, the cell cycle is inhibited. BCL-2 and BCL-XL positive cells are being reduced in number.

The goal was to reduce cancer mortality in smokers. However, it was discovered that cancer mortality indices in smokers were greater than in their corresponding controls. It has been suggested that a diet rich in beta-carotene, alpha-tocopherol, and selenium lowers the risk of stomach cancer, and that eating marine algae (particularly Phaeophyta) lowers the risk of some cancers.(Armstrong & Hearst, 1996).

In human breast cell lines like MCF-7, beta-carotenoids stop cell growth, stop the cell cycle at different points, and make the cells more likely to die after being treated with the carotenoids.Furthermore, as compared to synthetic-carotene, natural-carotene produced from Dunaliella salina caused greater rates of cell death in MDA-MB-231 breast cancer cells.(Gloria et al., 2014; Rocio Gomez, 2015).

Breast cancer in MDA-MB-231,HaCat,Beta carotene in cells is visible. When natural and synthetic sources were used to induce apoptosis, natural -carotene resulted in much greater rates of cell death than the synthetic version(Milani et al., 2017).

Treatment of human chronic myeloid leukemia and monocytic leukemia (U937) with beta-carotene revealed that at lower concentrations it functions as an antioxidant, while at greater concentrations it acts as a pro-oxidant. At that concentration, beta-carotene also stopped HL-60 leukemia cells from entering the G1 phase and drastically decreased their viability. In fact, raising the quantity of beta-carotene increases the number of apoptotic bodies.(Upadhyaya et al., 2007).

Cell cycle arrest in the G1 phase, activation of apoptosis, and antioxidant capabilities are shown in leukemia illness (in vitro) in U937 and HL-60 cell lines(Milani et al., 2017).

Asubstantial link was discovered between a high level of serum beta-carotene and the risk of prostate cancer(Karppi et al., 2012).

Beta-carotene's pro-oxidant characteristics induce apoptosis in the WiDr cell line.It protects against gastric cancer. appears in the AGS cell line. In addition, Beta-carotene hepatocarcinoma (in vitro) inhibits proliferation and decreases VEGF production in B16F10, SK-Hep1 and PC-3 cell lines in prostate cancer.(Milani et al., 2017)

8.21.2 Curcumin

Curcumin inhibits leukemia in Bel7402, HL60, and SGC7901 cell lines; in female BALB/c athymic (nu+/nu+) mice, curcumin inhibits leukemia. The growth of cancer cells was slowed, the activity of telomerase was cut back, and the length of their telomeres changed.(Milani et al., 2017).

Curcumin inhibited breast cancer growth in MDA-MB-435 cells and female athymic nude mice. Here, apoptosis is increased. Suppression of NF-B reduced breast cancer metastasis to the lungs.In addition, curcumin induced human ovarian cancer cells, CaOV3 cells, which triggered AMP-activated protein kinase (AMPK) activation, and HPV infections, which cause cervical cancer.(Lai et al., 2010).

C50 for crocin (2mM) in female C57BL/6 mice, TC-1 cell line, reveals induction of a sub-G1 peak, apoptosis anti-tumor impact, cell growth prevention, chemotherapeutic drug. In CaOV3 cells treated with 50 M Curcumin, it promoted AMPK activation in vitro. Besides, curcumin increases inhibition of tumor development in KU-7 and 253JB-V cell lines and in athymic nude mice. Also, dietary therapy of curcumin dramatically lowered the incidence of breast cancer metastasis to the lung. Curcumin reductase apoptosis in melanoma cells through a caspase-8 pathway in human bladder cancer cells and in skin tumors. On the other hand, at a dosage of 25 M, curcumin inhibited the development of bone marrow (BM) (which is derived from murine DC). Furthermore, a 1,000 mg/kg dose of curcumin causes small intestine cancer and liver cancer in Nrf2 knockout mice (-/-).liver and small intestine cancer. Hydrazinobenzoyl curcumin (HBC) inhibits A549 cell growth via autophagy in A549 cells. In addition to curcumin, tetrahydrocurcumin (THC) demonstrates action against colon cancer, which is more active than

curcumin in male B6C3F1 mice with 0.2 percent (THC) and 0.5 percent (curcumin) in their diet.(Milani et al., 2017).

8.21.3 Retinoic acid (Vitamin A)

was shown to have carcinogenic effects in the colon.Production of COX2 (a crucial enzyme in the synthesis of prostaglandins) has also been cited as an early and fundamental event in colon carcinogenesis.(Astorg, 1997).

8.21.4 Crocetin

suppressed (EGFR) activity and increased the Bax/Bcl-2 ratio in human pancreatic adenocarcinoma cell lines (e.g., MIAPaCa-2, BxPC3, Capan-1, and ASPC-1) to considerably decrease proliferation(Dhar et al., 2009).

Crocetin also has anti-proliferative effects in HT-29, HCT-116, SW-480, and NSCLC cell lines when given at a 3 mg/ml dose. Crocetin works as a chemopreventive agent against Benzo(a) pyrene-induced lung cancer by maintaining glycoprotein levels in the blood and tissues.Lung Cancer (in vivo): Cell growth in male Swiss albino mice is inhibited by 50 mg/kg body weight. Crocetin gastric cancer (in vitro/in vivo): HFSF-PI3, AGS, cell lines, and male Wistar albino rats with 200 mol/L dosage indicate activation of apoptosis and reduction of BCL-2/Bax mRNA ratio. Male Kunming mice (ALP) have low levels of crocin, Crocetin Liver Damage serum ALT, and alkaline phosphatase, AST.(Milani et al., 2017).

8.21.5 Astaxanthin

This significantly lowers the risk of colon adenocarcinoma activity. In vivo evidence of Astaxanthin's anti-colon cancer activity: inhibition of colon cancer by effects on the NF-B signaling pathway in male Crj: CD-1 (ICR) mice at a level of 200 ppm (no harm).(Capelli et al., 2013).

8.21.6 Lycopene

Topoisomerase inhibitors and lycopene work together in vitro. The Wnt-TCF action in breast cancer cells is inhibited without impacting normal cells. The processes involved in lycopene's tumor growth inhibitory actions in general(Preet et al., 2013).

Supplementing with lycopene may slow the progression of prostate cancer by increasing Cx43 gap junction protein levels, lowering IGF-1 levels, and increasing (IGFBP-3) levels(Kucuk et al., 2001b).

In prostate cancer, LNCaP 40 M, PC3 30 M in PC-3, LNCaP, and cell lineeffects on the body, Downregulation of androgen receptor (AR) transactivation and expression as well as AR-related cofactors such as (AP-1), NF-B, CREB, and CBP. LNCaP, PC-3, and lines development of human lung, endometrial, and breast cancer cells. Endometrial and breast cancer cells respond to insulin-like growth factors as autocrine mitogens. Natural Lung Cancer Lycopene 1.1 and 4.3 mg/kg body weight per day in male adult ferrets demonstrate the development of apoptosis and suppression of cell growth, which ensure protection against lung cancer. In lung cancer, a dosage of 50 ppm of lycopen inhibits lung neoplasian development in male B6C3F1 mice. Lycopene and genistein were known to be powerful antioxidants, and their co-relation provided the best protection against breast carcinogenesis caused by 7, 12-dimethylbenzanthracene. Breast cancer 10 M lycopene and beta carotene in MDA-MB-231, MCF-7, and MDA-MB-235 cell lines. Cell growth inhibition, cell cycle arrest at various stages, and apoptosis induction. Lycopene, alpha, and beta carotene Lung cancer and breast cancerWith 1-2 M Lycopene, Lycopene suppressed IGF-induced cell proliferation in NCI-H226 and MCF-7 cell lines; Lycopene is a more powerful suppressor than alpha and beta carotene.(Milani et al., 2017).

It has been proven that thermal processing improves the bioavailability and absorption of carotenoids, including lycopene, beta-carotene, and cryptoxanthin. Women with increasing circulation levels of these carotenes may have a lower risk of breast cancer.(Eliassen et al., 2012).

8.21.7 Crocin

It has been reported that crocin shows anti-breast cancer actions. It shows up in MCF-7 cells. Apoptosis induction and caspase-8 activation. Crocetin targeted two types of cancer cells, MCF-7 and MDA-MB-231. Here, the proliferation of crocein and crocetein is inhibited.(Milani et al., 2017).

8.21.8 Lutein and Zeaxanthin

High lutein and zeaxanthin consumption has been linked to a lower risk of skin carcinogenesis.

8.21.9 α-Carotene

There are two different types of carotenoids (clinical and In Chinese women, higher blood pressure of alpha-carotene and beta-carotene, as well as other vitamins, was linked to a decreased risk of cervical cancer.(Guo et al., 2015).

In the lab, alpha-carotene stops Lewis lung carcinoma from spreading, and when it's used with taxol, it reduces lung metastasis and tumor growth in C57BL/6 mice.

In SK-Hep-1 cells from human hepatocellular carcinoma and mouse lung carcinogenic cells, AC prevents cancer spread. The LLC-bearing C57BL/6 mice are a well-known animal model for studying how tumors start growing and how they progress to other parts of the body, like the lung.

Lewis lung cancer (LLC) and the combination of beta-carotene (AC) and taxol in C57BL/6 mice with LLC are studied in this study. The anti-metastatic effects of AC and taxol are looked at.

The impact of Alpha Carotene and Beta Carotene on LLC invasion and migration During 48 hours of incubation, AC strongly decreased LLC invasion, with inhibitory values of 33.5 percent (Pb0.5) for 12 hours, 42.2 percent for 24 hours, and 30.9 percent for 48 hours at AC 2.5 M. At the same dose as AC, BC had the same effect on invasion and migration at 12, 24, and 48 hours.

Incubation of LLC with AC for 24 hours dramatically reduced uPA, MMP-9, and MMP-2 activities in a concentration dosage pattern with MMP-9 inhibition of 38% (Pb.05) and mMP-2 inhibition of 32% (Pb.05) at 2.5 M AC. At the same dose, BC had a much weaker effect on uPA activity than AC did, but it was still weaker than AC.

At AC, incubation of LLC with AC enhanced TIMM-2 and TIMP-1 protein expression in an adosage pattern. Research says that incubation with AC raised BC protein levels to the same level as AC at the same dose, which is what happened when AC was mixed with AC.

AC reduced phosphorylation of JNK1, ERK 1 and 2, and JNK2 at 45 and 60 minutes of incubation, with 60 minutes being the most effective. The FAK and MAPK families' protein expression was unaffected by AC.

The combined therapy inhibited lung metastases by 49% more than the AC and taxol therapies alone. In comparison to the tumor-controlling group, the mixed treatment specifically slowed tumor growth. In mice, AC treatment had no impact on the growth of the primary tumor. Taxol treatment had a big effect on the size and weight of the primary tumors.

AC therapy alone raised TIMP-1 and PAI-1 protein expression but had no effect on FAK phosphorylation in lung tissues. MMPs are zinc-dependent endopeptidases capable of degrading all known extracellular matrix components (ECM).

In LLC, AC suppressed FAK and MAPK phosphorylation, followed by suppression of the ERK/p38/JNK pathways. When Alpha Carotene and Beta Carotene were given to mice at the same dosages, AC was more impactful than Beta Carotene in preventing carcinogenesis in the liver, lung, skin, and colon.

In mice, alpha-carotene reduces lung metastases while also increasing the inhibitory impact of taxol. Tumor development has been slowed by Taxol, a well-known anti-cancer medicine. After a 15-day treatment with AC and taxol, the tumor's volume dropped by 26.2 percent (Pb.05).(Liu et al., 2015).

8.21.10 Perillyl alcohol

It is a kind of alcohol. Anti-cancer properties In cancer, perillyl alcohol is both a preventative and a therapeutic agent. The researchers discovered that giving rats perillyl alcohol at a level of 1-2 g/kg reduced the frequency and variety of rectal aggressive carcinomas produced by the carcinogen azomethane injection. (Yang et al., 2020).

External perillyl alcohol has an anti-carcinogenic impact on the dermis. Tumor growth in Swiss Albino mice would most probably be the result of the ROS responses, which were seen in our study. In marine skin malignancies, the activation of apoptosis and the Ras cell growth pathway are reduced. This medicine was also good at fighting pancreatic cancer when it was taken in low doses that didn't hurt the host organism.(Koziol et al., 2014)

8.21.11 Geraniol

reduces the development of tumor cells in breast cancer patients. The G1 phase of the (MCF)-7 breast cancer cell cycle is blocked by geraniol, which limits tumor cell proliferation. Geraniol had no influence on the proliferation of MCF-10 normal breast epithelial cells, indicating that it has tumor-specific action. It also prevents prostate cancer from spreading to other parts of the body. Geraniol, according to the researcher, reduces the production of the HMG-CoA reductase gene in various tumor cells, which could be used in cancer therapy.Geraniol has the ability to inhibit AKT signaling, stimulate AMPK signaling, and suppress the mTOR signaling pathway. Prostate cancer responds to androgen restriction treatment at first, but castration-resistant prostate tumours grow later.(Yang et al., 2020).

8.21.12 Paclitaxel

When administered to ovarian cancer patients, paclitaxel may trigger the toll-like receptor 4 nuclear factor kappa B (NF-B) pathway and boost the expression of the ABCB1 gene, which is significant for understanding paclitaxel drug resistance. Paclitaxle was shown to be cytotoxic to SKOV3 cells with a viability rate of 38.2 percent for 1 mol/L and an apoptotic rate of 15.7 percent for 100 mg/l.(Yang et al., 2020).

8.21.13 Ursolic acid

Breast cancer cells are being treated (in vitro). A substance called ursolic acid may help to keep cancerous cells from dying by changing the Ras homolog gene family member. This may also help to keep cancerous cells from dying by changing the Ras homolog gene family member.It has anticancer properties and may promote tumor cell death. In this study, ursolic acid at low micromolar concentrations was found to boost anticancer activity by targeting gluconeogenesis in breast cancer cells with different phenotypes.

In vitro, inhibition of human osteosarcoma cell growth and apoptosis are induced in vitro. Ursolic acid may also slow down the growth and death of human osteosarcoma 143B cells by blocking Wnt/-catenin signaling, which may kill them.

According to the research, ursolic acid induces cell death in prostate cancer cells through associated tensin homolog-mediated cofilin-1 mitochondrial translocation and protein kinase/phosphatase. Ursolic acid is also synthesized into nanoparticles, which may boost bioavailability and anticarcinogenic activity. In vitro, colon adenocarcinoma is inhibited by canthaxanthin.

Canthaxanthin inhibits tumor human cell lines such as SK-MEL-2 melanoma and WiDr colon adenocarcinoma. These findings imply that carotenoids may be effective tumor growth inhibitors, but not in normal cells. Tumor cells are thought to have a lower rate of apoptosis than normal cells.(Yang et al., 2020).

8.21.14 Citral

It has inhibited the development of Cyclooxygenase-2 mRNA and enzyme caused by LPS in a dosage pattern. Citral's anti-inflammatory properties may be due to some of these actions(Koziol et al., 2014).

8.21.15 Limonoids

Breast cancer tumors that had undergone regression after being treated with limonene had significantly higher levels of mannose 6-phosphate/insulin-like growth factor II receptor and TGF-1, suggesting that these molecules are involved in the cancer regression caused by this monoterpene. -Limonene and -Perllyl alcohol have also been shown to have chemotherapeutic impacts in the diagnosis of rat mammary tumors.(Koziol et al., 2014).

8.21.16 (+)(-)Limonene

It was identified in chemically produced epidermis, pulmonary, forestomach, and mammary tumor model systems throughout both the start and promotion phases of carcinogenesis, as well as in the skin and lungs of healthy mice. Because limonene preferentially inhibits small G proteins, which are critical in signal transmission, (+-limonene)-induced tumor regression has a lethal impact.(Koziol et al., 2014).

9 ClinicalTrial

9.1 β-carotene

- Beta carotene has been shown to have antioxidant action in clinical experiments on Chinese women with cervical cancer, which is advantageous in lowering the development of cervical cancer.(Guo et al., 2015).
- According to the findings of research conducted on Finnish men with prostate cancer, a high amount of beta-carotene in the blood was connected with a decreased development of prostate cancer(Karppi et al., 2012).
- clinical trials with new stage of HCV were linked to a lower level of carotene, serum retinol, and retinol binding protein 4 (RBP4).(Kataria et al., 2016).
- A deficiency of omega-3 fatty acids, zinc, alpha-tocopherol,vitamin C, vitamin D, carotene, and lutein was connected to neurovascular AMD in a study of individuals with age-related macular degeneration (AMD). Low intakes of retinol and cryptoxanthin were shown to have no influence on the condition(Aoki et al., 2016).

9.2 Crocin

- A clinical study on adult outpatients with depression found that there were no adverse effects and that the drug had an antidepressant effect(Noorbala et al., 2005).

9.3 Curcumin

- Clinical studies on pancreatic cancer patients show a loss of subcutaneous fat and muscle when compared to untreated people.(Schaller et al., 1999).

9.4 Biscuits with Curcuma

- Cardiovascular disease in healthy males in clinical experiment Curcuma biscuits are a good example of this. Prevention of cardiovascular disease through lowering total cholesterol and LDL cholesterol.(Madaric et al., 2013).

9.5 Zeaxanthin/ Lutein

- It is seen in AMD patients with age-related Macular Degeneration. It's strongly linked to a lower risk of AMD.(Seddon et al., 1994).
- It demonstratesthat healthy women less than 75 years of age who have age-related macular degeneration are protected from intermediate AMD(Hutchinson, 2006).
- Overall, there is no statistical difference between AMD patients with nonAMD patients.(Outcomes & Registration, 2020).
- In type 2 diabetic patients who have Diabetic Retinopathy.Lutein/ zeaxanthi has potent preventative and therapeutic benefits.

9.6 Lycopene

- Following the lycopen clinical trial on men with prostate cancer, the chance of prostate cancer is reduced(Giovannucci et al., 2000).
- In a stage 2 randomized clinical study on individuals with prostate cancer prior to prostatectomy.It was discovered that (with no adverse effects) IGF-1 levels are reduced, IGFBP-3 levels are increased, and tumor development is reduced(Kucuk et al., 2001a).

- Nonsmokers and smokers with oral cavity and pharynx cancer should limit their intake of foods with low plasma lycopene levels, which are linked to a higher risk of death.of death(Susan T Mayne et al., n.d.)
- It may offer protection against digestive tract tumors in those with digestive tract cancer(Franceschx et al., 1994).
- HPV infection in women Dairy products There was a statistically significant negative relation between HPV presence and plasma cis-lycopene intentness . It has a tumor commutation of 56%.(Sedjo et al., 2002).
- In men with atherosclerosis, a high blood lycopene content is linked to a significant amount of carotid atherosclerosis(Rissanen et al., 2003).
- Healthy people with CVD have improved endothelial (vascular) function(Serg et al., 2014).
- The presence of healthy individuals is evident. Natural and synthetic lycopene are both good sources of lycopene(Hoppe, 2003).

10 Conclusion

In conclusion, carotenoids are essential components of all photosynthesis and possess unique photosensitizing and antioxidant characteristics. Isoprenoids are organic compounds having an eight basic structure and a C40 backbone. It belongs to the isoprene family. A unique set of colors known as carotenoids may be derived from natural sources.They are not just accountable for a vast diversity of natural coloration, but they also serve important biological functions. Carotenoids' health benefits in nutritional science have become more visible in recent times. In this review, carotenoids were studied for their structure, biosynthesis, metabolic engineering, and antioxidative properties. It is essential for pharmacological action as well as involvement in the light-harvesting process, so it performs a range of functions. It is their function as pigments that allows them to extend the spectrum while also protecting it from over-excitation and oxidative products. When taken as a supplement, carotenoids have indeed been demonstrated to defend against a number of cardiovascular disorders, as well as against oxidative stress and aging in general, and other medicinal activities, including anti-cancer and anti-inflammatory actions. Because the field of study into the function of carotenoids is so vast, there is a constant need for new research in this area of investigation.

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