REVIEW ARTICLE

Plant pigments as dietary anticancer agents

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Abstract

Present review article explains the dietary use of plant pigments and therapeutic effects against cancer. Important plant pigments such as anthocyanins, lycopene, carotenoids, chlorophyll, and betalains are explained for their anticancer effects. Plant pigments are secondary metabolites which obstruct cancer cell proliferation; stop growth and cell division in cancer cells. These inhibit cellular processes in cancer cells such as signaling pathways, cell cycle, induce apoptosis, and autophagy. Besides, anticancer activity these also assist in controlling high blood pressure, obesity, hyperglycemia, hypercholesterolemia, and restore cardiovascular problems. A full series of pigments is available in various plants families which might show protective effects against cancer. Plant pigments are edible, nutritionally rich and therapeutically suitable. Due to their health-promoting effects there is a growing public interest to consume green vegetables, fruits, sprouted seeds, pigmented cereals, and processed low energy antioxidative functional food. For widening their use, these could be harvested using recombinant gene technology to add to processed foods as a coloring agent. Plant pigments as natural plant products or its by-products are highly useful for the development of a large variety of functional foods, digestive ingredients, additives, as well as cosmetic products. These could be naturally added to genetically suitable modified foods by applying genomic tools. No doubt plant secondary metabolites will also fulfill needs of present-day medicine and show great promise for the future.

Key words: Anthocyanins, anticancer agents, betalains, carotenoids, chlorophyll, lycopene, plant pigments

INTRODUCTION

Cancer is a complex disease that shows abnormal cell growth with the invasion of surrounding cells and tissues. Cancer is caused by a progressive accumulation of multiple genetic mutations which are evoked due to environmental stress, microbial infection, food adulteration, smoke, tobacco, ionizing radiation, heavy metal exposure, and multiple genetic reasons. Approximately 5–10% of cancers are due to inherited genetic defects inherited from parents. Cancer is preventive if proper care and therapeutic dietary measures are maintained. By avoiding smoking, alcohol drinks, narcotics, and drugs reduces the chances of cancer. Although radiation therapy, surgery, chemotherapy, and targeted drug therapy are most prevalent methods to fight against cancer, these impose severe side effects and prove costly. However, the use of healthful foods mainly green fresh vegetables, fibrous, sprouted beans, red rice, and low salt diet, and supplementation of plant pigments in the diet is good for health. Pigments are secondary metabolites which provide different colors to plant leaves, flowers, fruits, stem and roots, and other vegetative tissues. Pigments have the primary function of photosynthesis as they capture radiant energy of sun and convert it into organic food. These also perform an important function in maintaining vitality, growth, and development of the plant. As functional food consumption of plant pigments promote health and reduce the risk of chronic diseases mainly cancer. Pigments act as bioactive agents against skin diseases and act as antioxidants, anti-inflammatory, anti-analgesic, and chemopreventive agents against cancer. Carotenoids show cytotoxicity to cancer and tumor cells, bacteria, and viruses. These are free radical quenchers, and inhibit progression of cancer pathway by activating anti-angiogenic and protein synthesis. Anthocyanin and phenolic pigments show

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cell-protective effects, inhibit tyrosine activity and obstruct initiation of malignant melanomas. Beta-carotene and lycopene curcumin/anthocyanin showed antitumor activity. Other plant pigments such as lutein, astaxanthin, violaxanthin, and antheraxanthin are good antioxidants and show cell protective activity. Apigenin, nerigenin, and flavonoids pigments found in *Sorghum bicolor* prevent colon cancer. Anthocyanin protects against colorectal cancer by inducing cell cycle arrest, modulating, anti-proliferative apoptotic mechanism. Anthocyanin repairs and protects genomic integrity. Anthocyanidins exert anti-estrogenic ability and cut down the rate of hormone-induced adverse effects in human. Healthy dietary practices with antioxidants boost up the immune and endocrine system.

Plant pigments are secondary metabolic compounds which impose specific coloring effects in plant tissues.[1] These are known as biochromes[2] and are good source of dyes. The primary function of pigments in plants is to capture photons falling in sunlight for photosynthesis. Usually, green pigment chlorophyll along with several red and yellow pigments help to capture light energy and photons are used in photosynthetic pathways to produce organic food. There are many different plant pigments, which found in different classes of organic compounds. Fruits and green vegetables possess ample amount of pigments whose consumption lower down risks of several cancer types. Colored fruits, leaves, seeds, and vegetables contain chemopreventive compounds which contribute antioxidant, anti-inflammatory, and anti-angiogenic activity. Pigment rich green or ripe fruits anti-oxidative activity and do cancer prevention.[1] Berry fruit shows anti-oxidative activity and produces age-associated stress.

Naturally, plants possess yellow, green, pink, purple, and white, and red pigments, most of them found in vegetative tissue.[3] Green leaves contain green pigment chlorophyll whose richness decides freshness and health efficacy of leafy vegetables. In nature genetic mutants of yellow and white pigments are available. In particular, phenolic flavonoids and terpenoid carotenoids, but also rare compounds such as curcumin and betalain, form this group of biochemical agents used in animal nutrition. Besides, phenolic flavonoids and terpenoids/carotenoids, few rare organic compounds such as curcumin and betalain [Figure 1], are also isolated from plants and are used in animal nutrition. Phenotypic changes in carotenoids also found in vegetative tissues, but levels of biosynthetically related isoprenoids such as tocopherols, ubiquinone, and plastoquinone.[4] Green plants also possess several different classes of bioorganic compounds, i.e., terpenoids, triterpene acids, phenolic acids, hydroquinone, flavonoids, hydrocarbons, sterols, fatty acids, tocopherols, and inorganic compounds but pigments show best anticancer[5] and anti-melanogenesis efficacy [Table 1].[3]

Few vegetables like tomato (*Solanum lycopersicum*) are rich in anthocyanins and lycopene. These are polyphenolic

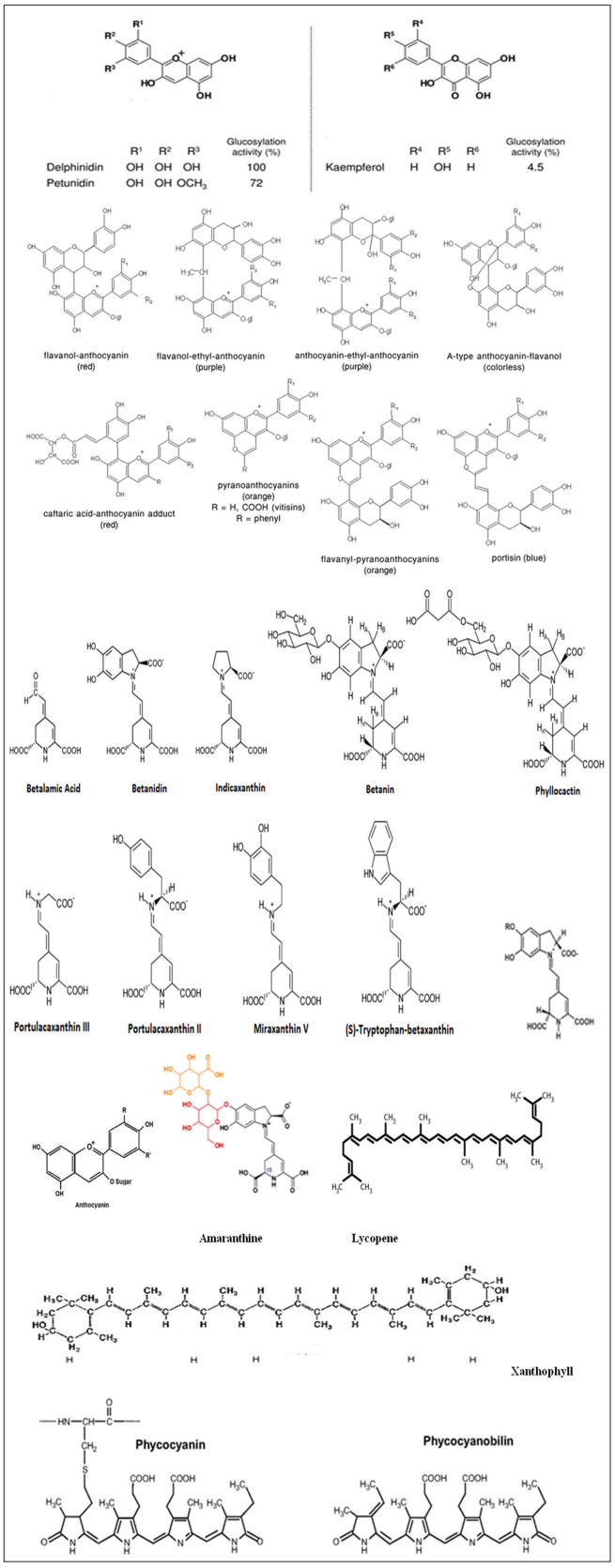

Figure 1: Chemical structures of various plant pigments

pigments found in peel, seed, and pulp and show strong antioxidant activity[6] and anticarcinogenic activity.[7] *Psidium guajava* contains pigments which assist in fighting

Table 1: Various plant pigment types and their anticancer potential

Pigment	Chemical form	Source plants	Color	Anticancer activity
Flavonoids	Anthocyanin, chalcones, flavonols, proanthocyanidins, aurones water-soluble plant pigments	Produce many colors in flowers. Common in plants such as berries, eggplant, and citrus fruits. Present in certain teas, wine, and chocolate	Yellow, red, blue, purple	Antioxidant, chemopreventive/ chemotherapeutic agent, anticancer effects, repairs and protects genomic DNA integrity. antioxidant and free radical scavenging, antitumor, anti-atherosclerosis, hypoglycemic, and anti-allergic activities
Carotenoids	Carotene, xanthophylls, astaxanthin, neoxanthin, violaxanthin, antheraxanthin, zeaxanthin, lutein, and beta-carotene	Found in green plants vegetables such as carrots, Citrus fruits, mangoes, and other fruits. Fucoxanthin is a carotenoid derived from edible sea algae	Oranges, reds, yellows, pinks	Anticancer and antimetastatic
Betalains	Betacyanins and betaxanthins	Flowers and fungi various betalains and betaine (trimethylglycine or glycine betaine) pigments have been isolated from beetroot	Red to violet, also yellow to orange	Inhibit cell proliferation, very cytotoxic to HepG2 cells, decreased cancer cell proliferation and viability in MCF-7-treated cells
Lycopene	Acyclic carotene and carotenoid pigment found mostly in red fruits and vegetables such as red carrots, watermelons, papayas	Found in non-red foods such as asparagus and parsley and green leafy vegetables and some fruits	Bright red colored pigment plant pigment	Its consumption lower down blood pressure, and boost up immunity. It suppresses NF-□B signaling in human prostate and breast cancer cells. It shows anti-proliferative activity
Chlorophylls	Chlorophyll, found in the inner membranes of chloroplasts, cell organelles mainly membrane	All green plants	Green	Anticancer activity, cytotoxicity toward human squamous cell carcinoma, free radical scavenging, and anticancer activity
Phycobilins	Water-soluble photosynthetic pigments	Blue-green algae and cyanobacteria.	Red, yellow, and blue	regulates plant development, including seed germination, stem growth, leaf expansion, pigment synthesis, and flowering

cancer.[1] Anthocyanins and carotenoids found in Japanese blue tomato[8] are strong anticancer agents.[4] Natural pigments such as anthocyanin,[9] hypocrellin A,[10] theacitrin A-C,[11] carotenoids, and green photopigments are considered best phytomedicine for cancer prevention.[12] Anthocyanins are phenolic pigments show cell protective effects[8] and show cytotoxicity to MCF-7 tumor cells.[13] Pink colored pigments found in onion and leeks are also anticancer in nature.[14] Hypocrellin A is a well-known natural pigment and bioactive agent that is used to treat skin diseases.[10]

Plant pigments such as flavonoids, terpenoids, carotenoids, curcumin, and betalain show different coloring effects in plant tissues.[15] These are used as livestock feed additives.[15] Flavonoids such as anthocyanins and stilbenes have potential health benefits. Both share common phenylpropanoid precursor pathways.[13] There are different sources of pigments as anthocyanin is produced in transgenic tobacco (*Nicotiana tabacum*) plants.[13] Nor-abietanoid is isolated from *Perovskia atriplicifolia* Benth,[15] while green pigment from intact garlic (*Allium sativum* L.) cloves[16] and tanshinones

from *Salvia miltiorrhiza*, a diterpenoid pigments.[17] Bee pollen and honey is also good source of plant pigment. Bee pollen contains tocopherol, niacin, thiamine, biotin and folic acid, polyphenols, carotenoid pigments, phytosterols, and enzymes and coenzymes. Natural plant pigment such as β-carotene, lycopene, curcumin, and anthocyanins showed antitumor activities.[18] Artemisinin, an antimalarial agent, is also showed antitumor activity.[19] Anthocyanin pigment provides brilliant red color to the *Vaccinium macrocarpon* plants with other secondary plant metabolites (flavonols, flavan-3-ols, proanthocyanidins, and phenolic acid derivatives).[20] Rosmarinic acid nor-abietanoid is a phenolic compound isolated form *S. arti filicifolia,*[21] ginsenosides a tyrosinase inhibitor,[22] tanshinone pigments from *S. miltiorrhiza* rhizome and root,[23] diterpenoid pigments from Gardenia jasminoides show the capability to stop growing malignant melanoma.[24] Cis carotenoids are free radical quenchers.[25]

Few plant pigments such as azaphilone alkaloids, namely, chaetomugilides A-C isolated from *Chaetomium globosum* TY1, an endophytic fungus found in Ginkgo biloba showed cytotoxic activities against human cancer cell line HePG2.[26] Similarly, apigenin, naringenin flavonoids from *Sorghum bicolor,*[27] phenolics from berry fruits *Vitis vinifera*,[28] (-) epigallocatechin gallate from green tea,[29] and plyphenolic red pigment from *Solanum tubersoum s*howed *in vitro* inhibition of colon cancer.[30] Carotenoid derivative inhibits nuclear fraction factor kappa B activity in cancer cells.[31] Turmeric contains yellow pigment derived from curcumin shows neuroprotective effect while betacyanins, betaxanthins and betalains, and hypericin induce metastatic melanoma cell death.[32] Betanins are major compounds found in red and yellow beta root extract (*Beta vulgaris* L.) show anticancer effects against HepG2 cells.[33]

Plant Pigment Types

Plant pigments are different categories of biomolecules which include porphyrins, carotenoids, anthocyanins, and betalains. These selectively absorb certain wavelengths of light and reflecting others.[34,35] Plants contain six ubiquitous carotenoids: Neoxanthin, violaxanthin, antheraxanthin, zeaxanthin, lutein, and β-carotene.[36] Lutein is a yellow pigment found in fruits and vegetables and is the most abundant carotenoid in plants. Other less common carotenoids in plants include lutein epoxide (in many woody species), lactucaxanthin (found in lettuce), and alpha-carotene (found in carrots).[37] In cyanobacteria, important carotenoids which exist in the form of canthaxanthin, myxoxanthophyll, synechoxanthin, and echinenone [Figure 1]. Algal phototrophs mainly dinoflagellates contain peridinin as a light harvesting pigment. Carotenoids also found complexed within chlorophyll-binding proteins such as the photosynthetic reaction centers and light-harvesting complexes. Tomato contains red color due to the presence of lycopene.

Anthocyanins

Anthocyanins are the largest group of water-soluble plant pigments found in the plant kingdom. These belong to flavonoid class mostly red to blue in color. These found almost in all vegetative tissues of higher plants, including leaves, stem, roots, flowers, and fruit. These are most visible in the flower petals in many plant species.[34] These polyphenolic pigments [Figure 1] also found vegetables and provide them vivid red to blue. More than 635 anthocyanin variants have been identified in nature. Among which six are common aglycones and various types of glycosylations and acylations. Eleven types of anthocyanins were identified, including delphinidin, petunidin, and malvidin from blue tomato extracts.[8] Dietary consumption of anthocyanins is health promoting[38] because it exerts strong antioxidant activity.[8] Anthocyanins also possess anti-inflammatory and anticarcinogenic activity, cardiovascular disease prevention, obesity control, and diabetes alleviation properties.[38] Tomato (*S. lycopersicum*) peel, seed, and pulp of tomatoes are rich in anthocyanins and lycopene contents. Chokeberry *Aronia melanocarpa* is also rich in anthocyanins which showed anticancer properties in other cancers.[39] Chokeberry kills the cancer cells by non-apoptotic pathways. Anthocyanins rich plant foods assist in cancer prevention. Radish (*Raphanus sativus* L.) contains anthocyanin, glucosinolates, anthocyanidins, and isothiocyanates in mature taproot. The primary anthocyanidins present in the red and pink radish varieties are identified as pelargonidin and delphinidin, while the primary anthocyanidin in the purple radish variety was cyaniding.[40] Flavonoids or polyphenols also found in vegetables, fruits, and green tea [Figure 1]. These showed strong antioxidant properties and considered acting as cancer-preventing or anticancer agents.[41] Anthocyanins show inhibitory effects on the growth of some cancer cells.

Mulberry naturally contains a high amount of polyphenols and volatile compounds. These are used in alcoholic beverages for generating natural colors.[42] Besides, polyphenols and flavonoids are also used in alcoholic beverages. These bioactive compounds may act synergistically to promote health and reduce risk factors of chronic diseases. Anthocyanin-enriched sweet potato P40 protect against colorectal cancer by inducing cell-cycle arrest, antiproliferative, and apoptotic mechanisms.[43] *Solanum melongena* anthocyanin or delphinidin extracts showed no apparent genotoxicity and mutagenicity.[44] Anthocyanins can become an essential part of human diet[44] mainly used in the preparation of staple foods. *Pourouma cecropiifolia* fruit extract contains anthocyanin (monomeric anthocyanins delphinidin-3-O-beta-glucopyranoside, cyanidin-3-O-beta-glucopyranoside, and cyanidin-3-O-(6”-malonyl)glucopyranoside) which showed moderate cytotoxicity toward different cancer cell lines.[45] It is extracted contain polymeric pigments such as proanthocyanidin and two flavanol-anthocyanin showed cell growth-inhibitory effect. This significantly reduced the viability of HEp-2 larynx, MKN-45 gastric carcinoma, and

MCF-7 breast cancer cells.[45] Anthocyanins, plant pigments found in fruits and berries are chemopreventive because they could delay cancer development.[46] Anthocyanins, anthocyanidins 3-deoxyanthocyanidins [Figure 1] are flavonoids can be used as chemopreventive drugs [Table 1].[47] These showed anti-oncogenic effects including anti-proliferation, induction of apoptosis and inhibition of activities of oncogenic transcription factors, and protein tyrosine kinases. Similarly, 3-deoxyanthocyanidins isolated from *sorghum* seedlings are highly anti-cancerous in nature.[47] Eggplant (*S. melongena*) skin aqueous extract also contain anthocyanin (delphinidin) exhibit nearly similar effects.[44]

Anthocyanidins, the aglycones of anthocyanins, impart brilliant colors in many fruits and vegetables. These belong to flavonoid family represent substantial constituents of the human diet. These showed tumor cell growth inhibition and stop human cancer cell proliferation.[48] Anthocyanidins such as cyanidin, delphinidin, pelargonidin, petunidin and malvidin and anthocyanins, cyanidin-3-glucoside, cyanidin-3-galactoside, delphinidin-3-galactoside, and pelargonidin-3-galactoside showed strong anticancer effects in human cancer cell lines.[48] Anthocyanins could repair and protect genomic DNA integrity. Similarly, bioflavonoids mainly anthocyanine aglycones[49] showed estrogenic activity that might play a role in altering the development of hormone-dependent adverse effects. Blueberries and berries are rich in anthocyanins and are recognized by different names as black raspberry, red raspberry and blackberry, black currants, cherries, eggplant peel, black rice, concord and muscadine grapes, red cabbage, and violet petals. Berries mainly wild blueberry, bilberry, cranberry, elderberry, raspberry seeds, and strawberry are rich in anthocyanin pigments that are why all berry fruits possess broad-spectrum therapeutic and anticarcinogenic properties. These are beneficial in reducing age-associated oxidative stress, as well as in improving neuronal and cognitive brain function. These are novel anti-angiogenic, antioxidant, and anticarcinogenic agents.[50] Plant pigments such as phytoalexins and anthocyanin pigments in plants act as antimicrobial agents.[51] As anticancer agent anthocyanins obstruct signaling pathways in cancer cells, including mitogen-activated protein kinase, nuclear factor κB, AMP-activated protein kinase, and Wnt/β-catenin, and affect crucial cellular processes such as cell cycle, apoptosis, autophagy, and biochemical metabolism [Table 1].

Anthocyanins found in most plant parts provide them different color from the range of red, purple, or blue, depending on their pH, anthocyanins are partly responsible for the red and purple colors of some olives. Proanthocyanidins are linked to the beige color of the bread bean seed coat, and also to shades of black, red, brown, and tan. Apples, bine, pine bark, cinnamon, grape seed, cocoa, and grape skin and the grapes used to make most red wines which contain proanthocyanidins as most preferable color. The yellow color of flavonoid pigments also found chalcones in flowers and the organs of plants. Similarly, aurones found in flowers and some bark, wood or leaves provide a specific color to them. Few natural pigments, i.e., lutein, riboflavin, curcumin, β-carotene, gardenia yellow, and opuntia betaxanthins showed thermal stabilities and used as natural yellow colorants in various foods.[52] Contrary to this, betaxanthins and riboflavin degraded rapidly as temperature increased. Gardenia yellow and curcumin showed intermediate thermal stability.[52] Cyanidin and its glycosides belong to the anthocyanins, which are widespread class of water-soluble plant compounds. These are responsible for the brilliant color (red, orange, and blue) of fruits and flowers.[53] These are easily digested by humans and used in the preparation of red wines. Most cyanidins after absorption and metabolism show antioxidant, antimutagenic, and other protective activities within the human body. Plant origin cyanidins are considered good dietary compounds which play a potential beneficial role in human health [Table 1].[53] Citrus fruits contain important dietary carotenoids mainly terpenoids as major components. These also contain limonoids with different aroma provide different fruit coloration, bitterness, and aroma.[54] Citrus hassaku pericarp contains limonoids which showed anti-metastatic effect through inhibition of C-X-C chemokine receptor Type 4 and matrix metalloproteinase-9.[55]

Sweet oranges and mandarins are rich in carotenoids and showed marked differences in carotenoid composition. The pulp and juice sweet orange also contains carotenes (mainly lycopene and phytoene) while β-cryptoxanthin and phytoene predominated in mandarins. Citrus fruits also contain higher soluble bioactive carotenoids which have potential nutritional and health benefits. Most leafy vegetable, fruits, and green pods contain a high amount of these pigments; hence, these are utilized as green.[41] Besides, pigments fresh fruits also found rich in vitamins which also assist in conventional anticancer treatment. In addition, specific anthocyanin metabolites showed additive and synergistic efficacy.[56] Anthocyanin and stilbenes have potential health benefits, and both share common phenylpropanoid precursor pathway.[13] Anthocyanin also found accumulated in seedlings.[57] Hydroxycinnamic, flavonoids, and anthocyanins are added during finishing of Tempranillo wines to provide specific color and phenolic attributes to it.[58]

Lycopene

Lycopene (neo-Latin *lycopersicum*) is a red colored pigment plant pigment found in tomato plants. It is a bright red acyclic carotene and carotenoid pigment found mostly in red fruits and vegetables such as red carrots, watermelons, gac, and papayas [Table 1 and Figure 1].[59] Like all carotenoids, lycopene is a polyunsaturated hydrocarbon, i.e., an unsubstituted alkene. Lycopene contains 11 conjugated double bonds, normally in transconfiguration. Lycopene's 11 conjugated double bonds provide it deep red color and make it a strong antioxidant. Lycopene is a tetraterpene and is assembled from eight isoprene units that are composed

entirely of carbon and hydrogen.[60] It is insoluble in water. However, it does not show vitamin-like activity.[59] Lycopene also found in non-red foods such as asparagus and parsley[59] and green leafy vegetables, and some fruits. In plants, algae and other photosynthetic organisms, lycopene occurs in the form of an intermediate compound in the biosynthesis of many carotenoids, including beta-carotene [Figure 1]. It provides yellow, orange, or red pigmentation, which performs photosynthesis and photoprotection.[61] Due to its strong natural color lycopene is most usable color in industrial by-products or processed food materials of plant origin all lycopene-rich foods are inversely associated to diseases such as cancers, cardiovascular diseases, and diabetes, and its demand is increasing day by day.[62]

Lycopene is non-toxic and is supplementary part of human diet. Lycopene is not an essential nutrient for humans but is commonly found in the diet mainly from dishes prepared from tomatoes (foods highest).[60,61] Fruits and vegetables that are high in lycopene include autumn olive, gac, tomatoes, watermelon, pink grapefruit, pink guava, papaya, sea buckthorn, wolfberry (goji, a berry relative of tomato), and rosehip.[59] Tomato (*S. lycopersicum*) is rich source of lycopene, Vitamin C, potassium, and folic acid. It shows the ability for adenosine deaminase inhibition that plays an important role in the regression of tumor. Tomato also contains other active compounds, namely, neoxanthin, lutein, α-cryptoxanthin, α-carotene, β-carotene, cyclolycopene, and β-carotene 5, and 6-epoxide [Figure 1]. These components provide synergistic effect against various malignant threats and reduce the risk of various maladies such as obesity, hyperglycemic and hypercholesterolemic attributes, cardiovascular disorders, and cancer insurgences.[63] Lycopene consumption lowers down blood pressure and boost up the immune system and the nervous system. It is sensitive to sunlight, or drugs used for stomach ailments.[64] Intestinal absorption of lycopene is enhanced by the presence of fat and by cooking.[59] However, for better absorption of lycopene requires combining with bile salts and fat to form micelles.[59] Lycopene dietary supplements (in oil) may be more efficiently absorbed than lycopene from food.[59] Although gac (*Momordica cochinchinensis* Spreng) has the highest content of lycopene of any known fruit or vegetable[65-67] mainly tomatoes and tomato-based sauces and juices. The ketchup accounts for more than 85% of the dietary intake of lycopene for most people.[59] The lycopene content of tomatoes depends on species and increases as the fruit ripens.[67] Addition of ripe tomatoes during cooking also increases the concentration of bioavailable lycopene due to its thermal stability.[59,68] In processed tomato paste lycopene remains 4 times more bioavailable than in fresh tomatoes.[69] For obtaining the maximum amount of lycopene, hybrid tomato is prepared by making cross between the domestic and wild tomato species *S. lycopersicum* and *S. pimpinellifolium*.[6] Watermelon is also a good source of dietary lycopene, ascorbic acid, and total phenolics.[70,71]

Dietary consumption of carotenoids reduces chances of malignant brain tumors [Table 1]. These successfully stop tumor cells to invade the normal brain.[72] These are considered good chemoprevention agents. This property has been tested in most carotenoids such as β-carotene, a-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin, and astaxanthin.[73] Similarly, pinophilins A and B are hydrogenated azaphilones which are inhibitors of human cancer cell proliferation.[74] Lycopene also inhibits the cell proliferation and invasion of human head and neck squamous cell carcinoma.[75] Similarly, β-Carotene 9',10' oxygenase modulates the anticancer activity in TRAMP model.[76] Lycopene acts through inhibition of IκB kinase to suppress NF-κB signaling in human prostate and breast cancer cells[77] lycopene also found preventive against gastric carcinogenesis.[78,79] It shows anti-proliferative and apoptosis-inducing activity against three human breast cancer cell lines.[80] It affects PI3K/Akt signaling pathway in prostate cancer.[81] Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines.[82] Lycopene also showed barrier protective effects in human endothelial cells.[83] Its normal concentration obstructs cell viability and cell cycle progression in human cancer cell lines.[84] Lycopene synergistically enhances quinacrine action to inhibit Wnt T-cell factor signaling in breast cancer cells through anaphase-promoting complex.[85] Due to all such metabolic functions dietary use of tomato is good for health as it contains good amount of lycopene pigment tocopherols and ascorbic acid [Table 1].[86]

Tomato (*S. lycopersicum*) plants synthesize nutrients, pigments, and secondary metabolites that benefit nutrition and human health. The concentration bioactive compounds are strongly influenced by the maturity of the tomato fruit. Fully ripe tomatoes, guava, red grapefruit, papaya, rosehips, and watermelon also possess higher lycopene contents. Among all processed tomato products pasteurized tomato juice, soup, sauce, and ketchup contain the highest concentrations of bioavailable lycopene from tomato-based sources.[87] Lycopene is used for several industrial applications. Furthermore, supplementation of lycopene and eicosapentaenoic acid inhibits the proliferation of human colon cancer cells.[88] Lycopene, canthaxanthin, and astaxanthin share a similar structure to carotene and are beneficial in cancer and cardiovascular disease prevention [Table 1 and Figure 1].[89]

Chlorophyll

Chlorophyll is a green pigment that occurs in plant leaves and foliages, algae, and photosynthetic bacteria. It shows structural similarity to heme pigment found in mammals. Chlorophyll found in the inner membranes of chloroplasts, cell organelles mainly membrane enclosed structures within plant cells. Chlorophyll as a phytochrome absorbs or intercepts light or captures photons from sunlight and is used to drive

photosynthesis [Figure 1]. All land plants and green algae possess two forms of this pigment chlorophyll *a* and chlorophyll *b*. Kelps, diatoms, and other photosynthetic heterokonts contain chlorophyll *c* instead of *b*, while red algae possess only chlorophyll *a*. Chlorophylls degrade into colorless tetrapyrroles known as nonfluorescent chlorophyll catabolites.[90] As the predominant chlorophylls degrade, the hidden pigments of yellow xanthophylls and orange beta-carotene are revealed.

Green plants possess high chlorophyll contents and show free radical scavenging and anticancer activity.[91] Young plant leaves contain pheophorbide a catabolic product of chlorophyll that shows anticancer activity.[92] Similarly, chlorophyllin shows inhibitory effects against cancer cells and induce chemokine expression.[93] Similarly, pheophorbide a tetrapyrrole ethanolamide derivatives, (hematoporphyrin propylether ethanolamide [HPPEEA, 1] and pheophorbide ethanolamide) in combination with anticancer drugs shows potential anticancer[94] and anti-metastasis activities.[95,96] Similarly, anticancer activity is also reported in pheophorbide isolated from the edible red seaweed *Grateloupia elliptica* shows strong anticancer activity [Table 1].[97] Contrary to this, chlorophyll-derived dietary phototoxin and protoporphyria are neutralized by some anticancer proteins.[98] Chalepin (Ruta angustifolia L. Pers) induces mitochondrial-mediated apoptosis in lung carcinoma cells.[99] Chlorophyll found in green *Carica papaya* leaves shows cytotoxicity toward human squamous cell carcinoma.[100] Green plant extracts stop adhesion, invasion, and migration in SK-Hep1 human hepatoma cancer cells.[101] Photodynamic therapy shows synergistic effect with doxorubicin on multiple drug-resistant uterine sarcoma cell MES-SA/Dx5.[102] This also induces apoptotic cell death in murine oral squamous cell carcinoma *in vitro* and *in vivo*.[103] Na-pheophorbide also shows phototoxic effect toward osteosarcoma cells *in vitro* [Table 1].[104]

Betalains

Betalains are red or yellow pigments found only in the Caryophyllales (including cactus and amaranth) [Figure 1]. These are synthesized from tyrosine and water soluble.[105] They only occur in few plant families and always independently of anthocyanins. These are isolated from *B. vulgaris* L. and are responsible for the deep red color of beets. Various betalains and betaine (trimethylglycine or glycinebetaine) pigments have been isolated from beetroot. The betalains consist of two subgroups, red-violet (beetacyanin), and yellow to orange (betaxanthin) pigments. Among predominant betalains, two are betacyanins (betanin and isobetanin), and two betaxanthins (vulgaxanthin I and miraxanthin V). Betanin and vulgaxanthin I are major compounds found in red and yellow beetroot extracts. Specifically, the green beetroots contain apigenin, vitexin, vitexin-2-O-xyloside, and vitexin-2-O-rhamnoside, while the red beetroot is a source of betaxanthins and betacyanins.[106] Betalains such as carotenoids and flavonoids also seem to play an important role in attracting animals to flowers and fruits produce a similar range of colors. Betalains give rise to the distinctive deep red of beetroot. The composition of different betalin pigments can vary giving rise to breeds of beetroot that are yellow or other colors, in addition to, familiar deep red [Table 1].

The betalins are red pigments found in beets. These include betanin, isobetanin, betanidin, phyllocactin, indicaxanthin, hylocerenin, 2', O-Apiosylphyllocactin. These are are established food colorants. Both betacyanins and betaxanthins are classed as betalains. Betalains cause the crimson of amaranthus flowers (class of caryophyllales). Betalains are close in structure and in their synthesis to the animal pigment group melanins and eulamelanins in particular. The green beet (*B. vulgaris* var. cicla L.) and red beetroot (*B. vulgaris* var. rubra L.) contain phytochemicals that have beneficial effects on human health. C-Glycosyl Flavonoids from *B. vulgaris* cicla and betalains from *B. vulgaris* rubra showed strong antioxidant, anticancer, and anti-inflammatory activities.[106] Betalains through dietary use block the proliferation of tumor cells and inhibit their pro-survival pathways. Betanin-enriched red beetroot (Beta vulgaris L.) extract induces apoptosis and autophagic cell death in MCF-7 Cells.[107] Beetroot extracts showed cytotoxic effect on cancer cells. Betanin/isobetanin significantly decreased cancer cell proliferation and viability in MCF-7-treated cells. These also restore mitochondrial membrane and intrinsic and extrinsic apoptotic pathways.[107] Seed sprouts contain betacyanin made strong anti-inflammatory and anticancer activity.[108] *Beta vulgaris cicla*, BVc) and (*Beta vulgaris rubra*, BVr) extracts contain apigenin flavonoids, namely vitexin, vitexin-2-O-rhamnoside and vitexin-2-O-xyloside which showed antiproliferative activity on cancer cell lines.[109] Betanin inhibits cell proliferation show very high cytotoxicity to HepG2 cells [Table 1].[33]

Flavonoids

Flavonoids (derived from Latin word flavus which means yellow) are widely distributed plant pigments. Flavonoids found in flowers and fruits provide them strong colors which attract animal pollinators and seed dispersers. These are also found in lemons, oranges, and grapefruits. Mostly flavonoids are located in the cytoplasm and plastids. These are water soluble and commonly occur in vacuoles, membrane-enclosed structures within cells which also store water and nutrients. Interestingly, light absorption by other photoreceptive plant pigments, such as phytochrome and flavins, induces synthesis of flavonoids in many species. Anthocyanins yellow colored plant pigments belong to the most common class of flavonoids. Anthocyanins and proanthocyanidin and the reddish-brown pigment theaflavin found in tea which creates variable colors. Few flavonoids are visible only under ultraviolet (UV) light. Many processed foods, i.e., dark chocolate, strawberries, blueberries, cinnamon, pecans, walnuts, grapes, and cabbage contain flavonoids. These chemicals lower cholesterol levels, and many have antioxidant properties. One such flavonoid

fisetin (3,3',4',7-tetrahydroxyflavone) found in various fruits and vegetables such as strawberry, apple, persimmon, grape, onion, and cucumber. Fisetin is a chemopreventive/chemotherapeutic agent against cancer and other diseases.[110] Dietary consumption of flavonoids provides health benefits [Figure 1 and Table 1].

Carotenoids

In plants carotenoids found in roots, stems, leaves, flowers, and fruits. These are natural fat-soluble pigments mostly synthesized during fruit ripening and provide bright, red, orange, or yellow to plants. These tetraterpenoids found in the membranes of plastids, organelles surrounded by characteristic double membranes. Chloroplasts store carotenoids. In higher plants, carotenoids serve as precursors to the plant hormone abscisic acid. These perform light harvesting functions and assist in photoprotection (energy dissipation through non-photochemical quenching as well as singlet oxygen scavenging for prevention of photooxidative damage), and also serve as protein structural elements. These provide protection against excess light in plants. Few important carotenoids (β-carotene, lycopene, lutein, astaxanthin, violaxanthin, and antheraxanthin) are synthesized by many plants, fungi, and bacteria. Fucoxanthin is a carotenoid derived from edible sea algae.[111] Carotenoids are also used as a biomarker[112] and act as essential sources of retinol and Vitamin A for animals.[113] Carotene is a pigment that absorbs blue and indigo light and provides that rich yellow and oranges. The distinctive color of mango, carrots, fall leaves and yams are various forms of carotene a yellow colored pigment. This pigment is important to human diet, as the human body breaks down each carotene molecule to produce two Vitamin A molecules. Dietary use of carotenoids reduces the risk of cancer-related abnormalities in different tissues. Carotenoids are natural pigments. There is a growing public interest for the use of carotenoids as functional food due to their potential health benefits [Figure 1 and Table 1]. Carotenoids derivatives are topically used for sun protective and whitening purposes.

Phycobilins

Phycobilins are water soluble photosynthetic pigments. They lack in higher plants but found in red algae and the cyanobacteria. Similarly, phytochrome found in blue-green that regulates plant development including seed germination, stem growth, leaf expansion, pigment synthesis, and flowering [Table 1]. Phytochrome has been found in most of the organs of seed plants and free-sporing plants.

Seeds and Sprouts from Legume

Seeds and sprouts of various legumes crop are used as functional foods. These possess high nutritive value and contain amino acid, fiber, trace elements, vitamins, flavonoids, and phenolic acids. Consumption of seeds and sprouts lower down the risk of various diseases and exert health-promoting effects. Half-grown seeds and sprouts are rich in phenolics and flavonoids which show strong antioxidant activity.[114] Phenolic compounds are considered as good secondary metabolites for dietary use as they are synthesized by plants during normal development and in response to stress conditions. These are very popular among people as these improve and maintain their health status. These phytochemicals are derived from phenylalanine and tyrosine. Plant phenolics include simple phenols, phenolic acids, coumarins, flavonoids, stilbenes, hydrolyzable and condensed tannins, lignans, and lignins mostly occur in leafy vegetables, fruits, stems, and roots. In plant, phenolics act as phytoalexins, antifeedants, and attractants for pollinators. These contribute plant pigmentation and act as antioxidants, and protective agents against UV light. Phenolics contribute bitter taste, specific color, flavor, odor, and oxidative stability to the food products.

Pigmented Rice

The pigmented rice is mainly black, red, and dark purple rice, and contains a variety of flavones, tannin, phenolics, sterols, tocols, γ-oryzanols, amino acids, and essential oils. This is most popular food consumed in China, Japan, and Korea, and other Southeast Asian countries. It is used for strengthening kidney function and treatment of anemia. Pigmented brown rice and rice bran varieties showed anticarcinogenic potential.[115] It promotes blood circulation, removing blood stasis, treating diabetes, and used in traditional Chinese medicine. The extracts from pigmented rice are used as natural food colorants in bread, ice cream, and liquor as well as functional food. Anthocyanins are thought as major functional components of pigmented rice. Several anthocyanins have been isolated and identified from the pigmented rice including cyanidin 3-glucoside, cyaniding 3-galactoside, cyanidin 3-rutinoside, cyanidin 3,5-diglucoside, malvidin 3-galactoside, peonidin 3-glucoside, and pelargonidin 3,5-diglucoside.[116] These showed bioactivities including antioxidant and free radical scavenging, antitumor, anti-atherosclerosis, hypoglycemic, and anti-allergic activities.[116]

Fruits and Vegetables

Fruits and vegetables are also good source of antioxidants and dietary nutrients. These contain high contents of lycopene. Fruits such as autumn olive, gac, tomatoes, watermelon, pink grapefruit, pink guava, papaya, sea buckthorn, wolfberry (goji, a berry relative of tomato), and rosehip are rich in lycopene.[3] Tomato (*S. lycopersicum*) plants synthesize nutrients, pigments, and bioactive compounds that benefit nutrition and human health. Greenhouse-grown tomato varieties were also found rich in free amino acid and phenolic contents. These showed antioxidative and cancer cell-inhibiting activities.[97] Tomato

extracts promote growth in normal liver (Chang) cells and inhibit growth in lymphoma (U937) cells.[97] Red- and yellow-fleshed papaya (*C. papaya* L.) yellow fruits contained only trace amounts of lycopene, the latter was found to be predominant in red papaya (51% of total carotenoids).[117] Red papaya chromoplasts lycopene-rich tomato fruit (*Lycopersicon esculentum* L.) inhibit melanogenesis. Red and white pitayas are rich in flavonoids and polyphenol contents, these showed antioxidant and antiproliferative activities.[118] Similarly, peel of white and red pitaya is an important ingredient used in foods, nutraceutical and pharmaceutical applications. Both peel extracts also showed stronger antiproliferative activity against AGS and MCF-7 cancer cells.[118] The anthocyanin found in mature radish taproot reduce the risk of chronic disease through dietary intervention.[40] Fruits contain natural plant pigments such as β-carotene, lycopene, curcumin, and anthocyanins show strong antitumor activities. Red berries (fruits) *Tinospora cordifolia* (willd) contain berberine and lycopene pigments. These are used as nutraceuticals which show strong antioxidant activity.[119]

Microorganisms as Source of Dietary Pigments

Microorganisms also produce secondary metabolites such as mevastatin, lovastatin, epothilone, salinosporamide A which can be used for development of novel antitumor drugs. Prodigiosin (PG) is a natural red pigment produced by microorganisms *Serratia marcescens* and other Gram-negative bacteria. It shows strong antitumor potential.[120] Eight grifolin derivatives, involving three new monomers, albatrelins A-C (1–3), three novel dimers (meroterpenoid pigments), albatrelins D-F (4–6), and two known ones, 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methyl-3-penten-1-yl)-1,9-epoxy-6H-dibenzo[b,d]pyran, and confluentin were isolated from *Albatrellus ovinus*. In plants carotenoids play an important role in the photosynthetic process and photooxidative protection. Carotenoids are important as they influence the color (whiteness vs. yellowness) of the grain.[121] Nutritional and commercial improvement of wheat products can be done by modifying cultivars which might have high contents of bioactive compounds (total phenolic content, phenolic acids, flavonoids, flavonols, anthocyanins, and carotenoids). Phenolic compounds and carotenoids show string antioxidant and antiradical activity.[122] Anthocyanin extracts can be a suitable to produce functional foods with higher resistant starch content with potential human health benefits. Red yeast rice (RYR), the fermentation product of mold *Monascus purpureus* is modified to have more polyketide pigments and increased nutraceutical status.[123] RYR, the rice-based fermentation product of mold *M. purpureus* is a functional food. Its bioactive component monacolin K acts like synthetic drug lovastatin, without the severe side effects of the latter. Anthocyanins are natural pigments derived from the phenylpropanoid pathway. Most tomatoes produce little anthocyanins, but the transgenic purple tomato biosynthesizes a high level of anthocyanins due to expression of two transcription factors.[124] This high level of anthocyanins obtained in this transgenic tomato may provide unique functional products with potential health benefits. In potato (*Solanum tuberosum* L.), R2R3 MYBs are involved in the regulation of anthocyanin biosynthesis.[125] Carotenoids from vegetables, fruits, and other parts of higher plants and from marine sources are good anticancer, anti-obesity, antidiabetic, anti-inflammatory, and cardioprotective agents. Few most abundant marine carotenoids are fucoxanthin, astaxanthin, canthaxanthin, peridinin, fucoxanthinol, and halocynthiaxanthin which showed strong therapeutic efficacy not only against cancer but also other diseases.[126]

Pharmaceutics and Food Processing Industries

Secondary metabolites are proved strong antimicrobials. These also show antitumor, cholesterol-lowering, immunosuppressant, antiprotozoal, anthelmintic, and antiviral and anti-aging activities. Pigments such as PG and shikonin have antitumor activity, while violacein has anti-ulcer and antitumor activity and also acts as an antiprotozoal agent. Statins, in addition to, lowering cholesterol and low-density lipoprotein levels, also decrease elevated C-reactive protein levels independent of their cholesterol effects. Artemisinin is an antimalarial agent that also showed antitumor activity. Other natural products including those from plants (betulinic acid and shikonin), animals (bryostatins), and microbes (squalestatin and sophorolipids) have a multiplicity of potentially useful actions. Dietary supplementation of plant pigments or secondary metabolites can be used to prepare future medicine.[127] Phenolic compounds mainly hydroxycinnamic, flavonols, and anthocyanins are also to prepare tempranillo wines. These provide both color and phenolic attributes to the wine.[58] Anthocyanin pigments are made thermally stable by processing blueberries using metal complexation and cellulose nanofiber/sodium alginate layer-by-layer coating for retaining anthocyanin pigments.[128] Similarly, anthocyanin pigments are made thermally stable by processing whole blueberries, fruits, vegetables, meats, seafood, dairy, and egg products.[129]

Similarly, to optimize nutraceutical and medicinal use of red beet roots (*B. vulgaris* L.) are processed to enrich in betanin/isobetanin, decarboxybetanins, and neobetanin food-grade.[130] Flavonoids should be further exploited for the protection of food and beverages against light-induced quality deterioration eventually prevent quality loss.[131] Lettucenin sesquiterpenes contribute significantly to the browning of lettuce.[132] For making chlorophylls and carotenoids rich these are processed at intermediate stages of ripening.[133] Peppers are also rich in red pigments[134] while garlic green pigments. It is formed from pyrrolyl compounds.[135] For color stability non-saccharomyces yeasts are added during red must fermentation. Non-saccharomyces yeasts also generate pyranoanthocyanins and polymeric pigments after the addition of (+)-catechin and procyanidin B2 to fresh red grape must. The use of non-saccharomyces yeasts improves

the formation of stable pigments in red wines.[136] For wine color flavonols (flavonoid) and hydroxycinnamic acids are used for copigmentation.[137] Secondary metabolism contributes to the adaptation of a plant to its environment. In grape wine anthocyanins are also used as copigments and are used during wine storage.[138]

Polyphenolic pigments are added to wine for providing initial red-purple up to final red-brick nuances, and for color stability of aged wine.[139] Patatin a protein extracted from grape cultivars effect fining of white musts. It prevents browning and decrease haze during must settling because its effect on grape phenolics, brown pigments, and turbidity.[140] Plant phenolics have various industrial uses. These are beneficial to producers, processors, and consumers. By applying genomic tools in nutrition research many more bioactive agents can be obtained for dietary and therapeutic purposes.[141] For example, broccoli is genomically modified food that contains important biomolecules such as glucosinolates and plant pigments including kaempferol, quercetin, lutein and carotenoids, various vitamins, minerals, and amino acids. Broccoli and broccoli extracts also regulate the progression of cancer through anti-inflammatory effects (Son *et al.*, 2016).[142] Pigments such as polyphenols and flavonoids are used in alcoholic beverages. Dried raw ginseng roots possess ginsenoside that provides light color and its consumption shows antiproliferative activities.[143]

CONCLUSION

Fruits and vegetables such as tomato, citrus fruit and red rice berries, pomegranate, grapes, mango, carrot and sprouted seeds, micro-organisms, and algae are good source of pigments. These pigment rich foods are not only work against cancer cells but also show therapeutic effects against large number of human diseases and have multiple health benefits. Pigments found in berry fruits serve as antimutagenic agents. Seeds and sprouted legumes are rich source of vitamins, trace, elements, flavonoids and flavonic acids lower down risk of cell invasive diseases, and exert health promoting effects. Anthcyanin found in pigmented rice and fisetin flavonoid behave as chemopreventive agents who effectively work against cancer and other diseases. Although there are several sources of natural pigments from various plant species, genetically suitable modified foods may suffice this supplementary need easily if produced at large scale by biopharma and food industries. However, by adopting biotechnological methods genetically suitable cultivars of tomato, potato, berry fruits, grapes, carrots, onions, leeks, rice, radish, watermelon, turnip, black berries, mustard, olive, citrus, orange, mango, and jamun could be grown in glass houses. Thus, a full series of pigments is being made available from plant sources which might have anticancer activity, high thermal stability, photodynamics, and molecular efficacy against cancer cells. Edible food coloring should have a complete spectrum of various pigments types which are nutritionally and therapeutic suitable should identify, isolated and commercialized. Pigments breaks down contrive to produce two molecules of Vitamin A and red pigments. These could become essential part of fruits and that could promote human health, produces, processors, and consumers. Hence, processed foods contain high content of pigments could provide therapeutic target by supplementing safe dietary levels to prevent cancer and either wide range of diseases. Food processing industries are using biotechnologically generated phytopigments mainly flavonols, flavan-3-ols, proanthocyanidins, and phenolic acid derivatives to make by-products derived from foods more attractive edible and metabolically safe. Further, plant by-products are highly useful for development as functional foods, nutraceuticals, food ingredients, additives, and also as cosmetic products. No doubt plant secondary metabolites will also fulfill needs of present day pharmaceuticals, food materials and cosmetics and show great promise for the future.

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