Nutraceuticals in Cancer Therapy

11

Challenges and Opportunities

Shaimaa Fayez, Iriny M. Ayoub, Nada M. Mostafa, Ashaimaa Y. Moussa, Mariam I. Gamal ElDin, and Mohamed El-Shazly

Contents

Abstract

Cancer is known globally as a fatal disease with only minor progress done in reducing its morbidity and mortality. Still the exact reasons that predispose to cancer are not well defined; however incorrect diet, genetic makeup, and environmental factors could be considered as risk factors. Over 95% of cancers are triggered by lifestyle and might take up to 20–30 years to develop. Natural products have long been considered as enriched source of anticancer agents with diverse constitution, configuration, and bioactivities. Within the cancer field of research, many drug products in the market have been discovered from nature, by making modifications to the structures of the isolated natural products or by taking them as lead compounds to synthesize novel scaffolds.

S. Fayez · I. M. Ayoub · N. M. Mostafa (✉) · A. Y. Moussa · M. I. Gamal ElDin
Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
e-mail: nadamostafa@pharma.asu.edu.eg

M. El-Shazly (✉)
Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

Department of Pharmaceutical Biology, German University in Cairo, Cairo, Egypt
e-mail: mohamed.elshazly@pharma.asu.edu.eg

S. Chakraborti (ed.), *Handbook of Oxidative Stress in Cancer: Therapeutic Aspects*,
https://doi.org/10.1007/978-981-16-5422-0_15

Nutraceuticals are phytochemicals derived from dietary or herbal origin. They can significantly induce apoptosis in cancer cells hence justifying their use, in many circumstances, in combination with chemotherapy. Stilbenes, flavonoids, carotenoids, and sulfur-containing compounds are among nutraceuticals with prominent anticancer activity. In this chapter, we shed light on the clinical significance of the different nutraceuticals on different cancer types such as gastric, breast, ovarian, and skin cancers.

Keywords

Nutraceuticals · Flavonoids · Sulforaphane · Carotenoids · Resveratrol · Curcumin · Diet

Introduction

The term "nutraceuticals" was first introduced in 1989 by Stephen DeFelice describing for the first time food components with a positive effect on human health either curing or preventing diseases. Nutraceuticals are sometimes known as food supplements or medicinal foods that show benefits in managing and preventing cancer. The term gained popularity in recent years and was adapted by many dietary supplement companies. However, further research is warranted, and molecular level studies are far from being enough (Kerschbaum and Nüssler 2019). Beyond various factors that manipulate tumors, nutrients and dietary element availability can affect the microenvironment and inhibit cancer cell division. Adjustments in diet permit targeting susceptible metabolic points in tumor growth or potentiating the effect of anticancer agents. Dietary patterns and lifestyle – though not fully understood – play key roles in human health and should be rigorously considered in therapeutic and research approaches.

Nutraceuticals and Cancer

Flavonoids and Polyphenols

More than 4000 flavonoids were discovered over the last century in food with plant origin (Gosslau and Chen 2004). These polyphenolic compounds could be classified based on the degree of unsaturation and substitution pattern in the central pyran ring to flavones, isoflavones, flavanols, flavonols, and flavanones (Fig. 1).

Catechins

Catechins (Fig. 2), such as epigallocatechin-3-gallate (EGCG) and epigallocatechin (EGC), are flavan-3-ols commonly found in several herbal extracts including tea, berry, and beans. EGCG was found to induce apoptosis *in vitro* in many cancer cell lines among them breast, colon, lung, and cervical cells. The tested doses (ranged from 20 to 100 μM) resulted in an altered expression of genes involved in the cell

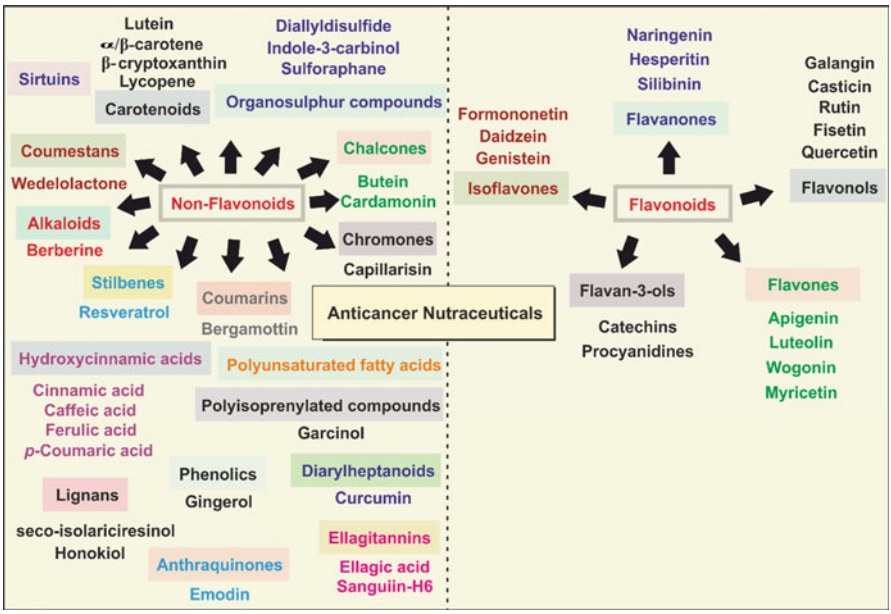

Fig. 1 Scheme showing the different classes of nutraceuticals with reported anticancer activities

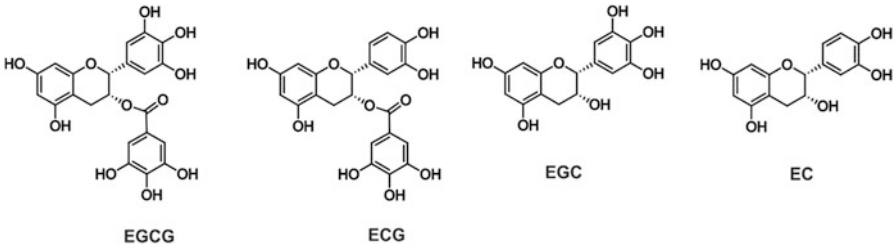

Fig. 2 Catechins in the green tea extract. EGCG: (-) Epigallocatechin-3-gallate; ECG: (-) Epicatechin-3-gallate; EGC: (-) Epigallocatechin; and EC: (-) Epicatechin

cycle; however, the exact molecular mechanism of EGCG remained unclear due to its poor bioavailability *in vivo* (Gosslau and Chen 2004). One study by Yang et al. (1998) showed that EGCG and EGC suppressed the division of the lung cancer cell lines H661 and H1299 (IC_{50} at ca. 22 μM). EGCG induced the production of H_2O_2 when co-incubated with H661, suggesting that this might be the cause for the growth inhibition and apoptosis induction seen by EGCG *in vitro*. The cytotoxicity of EGCG was found to be selective only to cancer rather than normal cells, which was clearly seen in Caco-2 (colorectal carcinoma) and Hs578T (breast cancer) compared with their respective normal cells (Chen et al. 1998). This selectivity involved NF-κB pathway through the inhibition of NF-κB/p65 complex protein. The cutch tree (*Acacia catechu* Willd.) extract is rich in its catechin content, which

promoted apoptosis in HT-29 (human colorectal adenocarcinoma) cells by increasing the activities of caspases-3 and -9 without affecting the viability of healthy cells (Chiaino et al. 2020).

EGCG reduced the expression of cancer stem cell biomarkers like aldehyde dehydrogenase-1A1 (ALDH1A1 is involved in the conversion of retinaldehyde – a metabolite of retinol – to retinoic acid, which regulates the transcription of genes involved in cell proliferation and apoptosis) and zinc finger protein SNAI2, which plays an important role in the differentiation and migration of cells. The same study revealed that EGCG knocked down the transcription of AXL receptor tyrosine kinase, which promotes the immune escape and drug resistance of cancer cells. EGCG showed more potency than EC in the inhibition of the growth and proliferation of the highly resistant triple-negative breast cancer cell line MDA-MB 468 especially after 24 h of exposure to 500 μM of EGCG (Mahadeo 2020).

In ovarian ES-2 carcinoma cell lines, catechins inhibited the metastasis and the epithelial–mesenchymal transition through the interference with the transforming growth factor-β pathway (TGF-β) (Sicard et al. 2020). Furthermore, EGCG and EGC significantly inhibited the expression of breast cancer resistance proteins in cancer cells (BCRP is an ABC efflux system first cloned from a multi-resistant breast cancer cell lines). The growth inhibition of catechins to the non-small-cell lung cancer A549 cell line was attributed to the overexpression of the cyclin-dependent kinase inhibitors p21 and p27, which act as tumor suppressors through promoting cell cycle arrest. A combined mixture of black tea and *Citrus reticulata* peels inhibited the proliferation and metastasis of hepatic cancer cells by affecting the PI3/AKT signaling cascade (Wen et al. 2020).

Studies on the targeted delivery of catechin hydrate in the form of chitosan-coated polylactic-coglycolic acid nanoparticles were conducted for the safe treatment of lung cancer. A cohort study by Zhang et al. showed an inverse correlation between tea consumption (green/black) and the risk for breast cancer (Zhang et al. 2020a). Depending on the dose (10 mg/day isoflavones) and the stage of breast cancer, flavonoids were found to affect the epigenetic machinery in breast cancer by inhibiting DNA methyl transferases and increasing the expression of tumor suppressor genes. In murine breast cancer cells (4T1), EGCG significantly inhibited the growth and division of cancer cells *in vivo* and *in vitro*. It additionally reduced the accumulation of myeloid-derived suppressor cells (MDSC, a type of immunosuppressive cells), which contribute to tumor initiation and propagation through increased expression of Arg-1 and increased production of ROS, NO, IL-6, TGF-β. This result was reported earlier by Santilli et al. (2013), showing the effect of polyphenon E (EGCG acts as its major ingredient) on MDSC in neuroblastoma animal model.

Epicatechin was investigated for its antitumor effect on breast cancer cells *in vitro*. The compound reduced the viability of MDA-MB-231 and MCF-7 through the induction of apoptosis, the upregulation of the death receptors 4 and 5 (DR4 and DR5), and the increased production of ROS in cancer cells. Dimeric ECGC and EGC inhibited the growth of five different colorectal cancer cell lines *in vitro* in a dose- and time-dependent manner by the induction of apoptosis and cell cycle arrest in the G_2/M phase. On the molecular level, ECGC and EGC dimers inhibited the

phosphorylation of epidermal growth factor receptor (EGFR) at the tyrosine residue 1068, therefore preventing its activation (Zhu et al. 2020).

Green tea and EGCG inhibited the growth of several human prostate cancer cell lines, resulting in a dose-dependent inhibition of cell growth along with cell cycle arrest. The induced apoptosis with no effect on normal cells. Studies on animal models showed that standardized green tea polyphenols delayed the development and progression of prostate cancer when administered in drinking water. EGCG downregulated the pro-inflammatory pathways, the insulin-like growth factor, and multiple kinases and diminished the effects of androgens in cell culture as well as in animal models (Johnson et al. 2010).

EGCG treatment inhibited UVB-induced infiltration of leukocytes that play vital roles in the promotion of skin tumors in multistage skin carcinogenesis. EGCG prevented UVB-induced immunosuppression, a risk factor for photocarcinogenesis, by inducing interleukin-12 (IL-12). The topical treatment with EGCG prevented photocarcinogenesis in wild-type (C3H/HeN) mice through an IL-12-dependent DNA repair mechanism; however, no effect was observed in IL-12 knockout mice (Meeran et al. 2006).

EGCG inhibited cell proliferation in gastric cancer cells under a state of hypoxia and induced apoptosis in a dose-dependent manner. EGCG inhibited the mRNA and protein expression of MDR-1 and *p*-gp. Moreover, EGCG inhibited VEGF secretion and expression. EGCG significantly induced apoptosis and inhibited cell proliferation (Almatroodi et al. 2020).

Theaflavins and Thearubigins

Black tea extract is rich in polyphenols like theaflavins (Fig. 3) and thearubigins, which are the oxidized and polymerized products of catechins formed during the processing of black tea. They significantly inhibited carcinogenesis in animal models with colon, lung, and breast cancer. Theaflavins and related tea polyphenols reduced oxidative stress and inhibited the cytotoxicity induced by H_2O_2. They suppressed the DNA damage exacerbated by oxidative stress in RL-34 rat hepatic cells. Theaflavic acid protects the cells from the damaging effects of ROS by

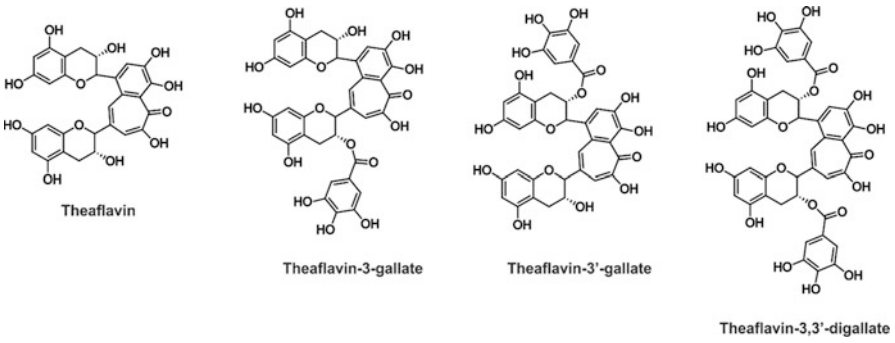

Fig. 3 Theaflavins in green tea extract

increasing the levels of superoxide dismutase, decreasing the content of lactate dehydrogenase, and downregulating caspase-3 levels, therefore inhibiting ROS-mediated apoptosis (Li et al. 2020). Theaflavins inhibit the epidermal growth factor in a dose-dependent manner through the inhibition of the transcription factor AP-1 (activator protein-1), which plays a significant role in cell differentiation, cell growth, and apoptosis (Dong et al. 1997).

The gallic acid portion, which exists in theaflavins possesses an antioxidant effect by suppressing the *in vitro* lipid peroxidation in the membrane of the erythrocytes and reducing the mutagenic effect induced by hydrogen peroxide. Cell-mediated immunity plays important role in compacting cancer. In a study performed by Chattopadhyay et al., they showed that PGE_2 induced apoptosis in $CD4^+$ cells (co-cultured with the breast cancer cell line MCF-7) through the inhibition of IL2Rγc, therefore suppressing body immunity. This process was reversed by theaflavins, which restored the levels of IL2Rγc and contributed to the survival of the immune $CD4^+$ cells (Chattopadhyay et al. 2009). On the other hand, theaflavins induced apoptosis in breast cancer cells having a mutation in p53 (highly resistant to chemotherapy) by the upregulation of the "Fas" death receptor, the activation of caspase-8, and the deactivation of Akt. Theaflavins inhibited the DHEA-induced cellular proliferation of MCF-7 human breast cancer cells *in vivo* and reduced the activity of aromatase enzyme. These polyphenolic natural products were highly efficient in treating the highly resistant breast cancer cells compared with tamoxifen (Way et al. 2004).

Flavonoids

A case-controlled study showed an inverse association between the intake of flavonoid-rich food containing quercetin and naringin (Fig. 4) and the risk of lung cancer (Le Marchand et al. 2000). Another case-controlled study showed an inverse link between the serum concentration of flavonoids (e.g., isorhamnetin, naringenin,

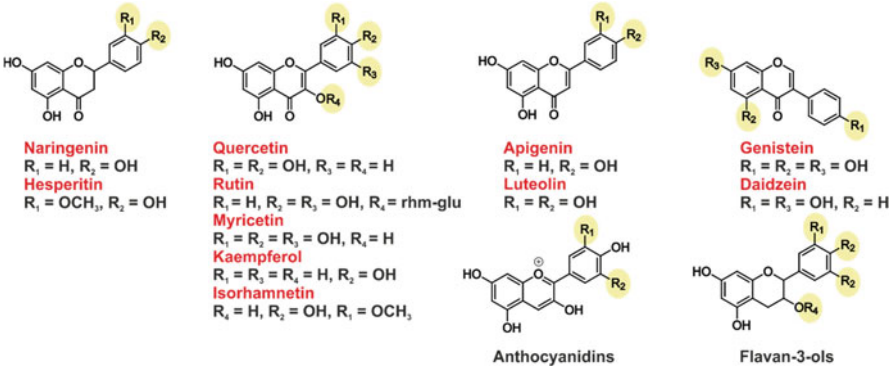

Fig. 4 Different subclasses of flavonoids including flavanones (e.g., naringenin and hesperetin), flavonols (e.g., quercetin, myricetin, rutin, isorhamnetin, and kaempferol), flavones (e.g., apigenin and luteolin), flavan-3-ols, anthocyanidins, and isoflavones (e.g., genistein and daidzein)

and kaempferol) and the risk of developing breast cancer among Chinese women (Feng et al. 2020). It was reported that flavonoids acted as epigenetic modifiers by regulating the epigenetic machinery including DNA methyltransferases and histone acetyltransferase in several types of tumors such as breast and prostate cancers. Radiotherapy is one of the treatment strategies for cancer. Flavonoids were found to act as radiosensitizers by improving the killing effect of ionizing radiation to cancer cells. Flavonoids from *Orthosiphon stamineus* Benth. inhibited the growth of MCF-7 human breast cancer cells and their tamoxifen-resistant subtype through the inhibition of PTPN1 protein tyrosine phosphatase non-receptor type 1B (To et al. 2020). *In vitro* and *in vivo* (on a lung cancer xenograft in BALB/c mice) investigations showed that flavonoids inhibited the growth and proliferation of A549 lung cancer cells in a dose-dependent manner through the induction of apoptosis, inhibition of cancer cell migration and invasion, as well as the downregulation of the mRNA expression of Wnt, β-catenin, and COX-2 proteins (Han et al. 2020). In a similar way, the flavonoids of *Epimedium koreanum* Nakai leaves inhibited the *in vitro* growth of A549 lung cancer cells with IC_{50} values ranging from 5.7 to 23.5 μM and the flavonoids in *Calendula officinalis* L. displayed a dose-dependent inhibition of the proliferation of MCF-7, AMJ-13, CAL-51, and MDAMB breast cancer cell lines in a selective manner. The flavonoidal compound, hydroxygenkwanin, suppressed the cell viability of non-small-cell lung cancer (NSCLC) by affecting the expression of the epidermal growth factor receptor, which is usually mutated in NSCLC (Leu et al. 2020). It is known that the dietary flavonol quercetin exhibited a cytotoxic effect on the breast cancer cells by enhancing apoptosis, decreasing the oxidative stress, inducing cell cycle arrest, and preventing cancer cell invasion and metastasis. *In vivo* studies on the flavanone metabolite bavachinin isolated from the seeds of *Psoralea corylifolia* showed that it significantly reduced the aberrant crypt foci in the colonic mucosa of Wistar rats at a dose of 200 mg/kg. Furthermore, it induced apoptosis and displayed an antioxidant effect by increasing the activity of superoxide dismutase, catalases, and glutathione reductase (Zhao et al. 2020a).

Non-flavonoidal Anti-cancer Nutraceuticals

Organosulfur Compounds

Sulforaphane (SLFN)

Sulforaphane (SLFN) (Fig. 5) is a sulfur-containing natural product commonly present in cruciferous plants such as broccoli and mustard. Several reports pointed to the efficacy of sulforaphane in the management of breast cancer through the induction of cell cycle arrest and apoptosis, suppressing the ROS, inhibiting the proliferation of cancer cells and in particular the cancer stem cells (CSC), which contribute to tumor initiation and progression. A study showing the effect of a combined treatment of SLFN and metformin (in a nano form) on different HER2+ breast cancer cell lines MCF-7, MCF-10, and BT-474 revealed that the combination was effective in accelerating apoptosis with high killing rate in BT-474 cells

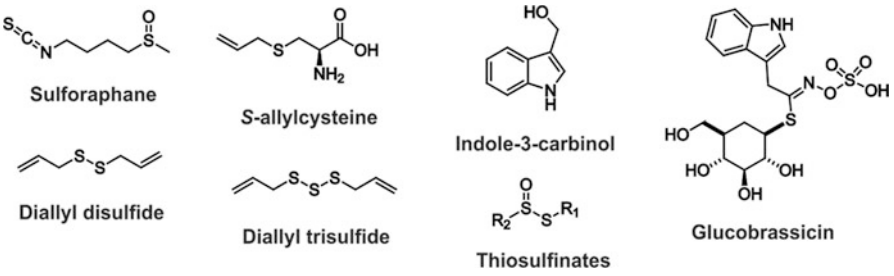

Fig. 5 Organosulfur nutraceuticals with cytotoxic activity

(Keshandehghan et al. 2020). SLFN is effective in eliminating the resistance developed after the hormonal therapy of ER+ breast cancer by CSC as it interferes with the STAT-3 signaling cascade, therefore improving the clinical outcomes in those patients (Simões et al. 2020). Furthermore, it inhibits breast cancer cell migration *in vitro* in a dose-dependent manner and reduces the expression of β-catenin and the biomarkers of epithelial–mesenchymal transition. SLFN was likewise effective in suppressing the tumorigenesis in colorectal carcinoma induced by carcinogenic heterocyclic amines via the upregulation of the expression of UDP-glucuronyltransferases 1A, which acted as a detoxification machinery for these substances (Hao et al. 2020). The combination of SLFN and microRNAs inhibitors (like peptide nucleic acids) promoted apoptosis in HT-29 colon cancer cell lines. The combination of the lignan magnolol and SLFN proved. This hybrid mixture strongly induced apoptosis by reducing the levels of the antiapoptotic protein Bcl-2 and by increasing the expression of the proapoptotic protein Bax (Tao et al. 2020). It was found that SLFN potentiated the cytotoxic effects of doxorubicin and cisplatin and reduced the incidence of resistance developed to them (Calcabrini et al. 2020). It increased the expression of the antioxidant enzyme, heme-oxygenase-1 in HCT116 colon cancer cells by activating Nrf2/ARE pathway, and showed the power to regulate the expression of different kinases like PI3K, Akt, and MAPK, which play key roles in cancer propagation. PI3K and Akt were also inhibited by a combination of SLFN and salinomycin antibiotic, which exerted synergistic effect on colorectal cancer cells by inducing apoptosis (Liu et al. 2020).

Glucobrassicin and Indole-3-Carbinol

Glucobrassicin belongs to the glucosinolates class of natural products and is found in many cruciferous plants including cauliflower, broccoli, and cabbages. The metabolic breakdown of glucobrassicin results in the release of indole-3-carbinol (I3C) (Fig. 5), which exhibited anticarcinogenic and antioxidant effects. A study by Nouriemamzaden et al. (2020) showed that I3C alone or in combination with the histone deacetylase inhibitor, vorionstat, modulated the expression of estrogen and progesterone receptors in many subtypes of triple-negative breast cancer cell lines. I3C similarly affected the growth of tumor cells and increased their sensitivity to tamoxifen therapy. Tetrameric I3C formulated in γ-cyclodextrin inhibited the proliferation of breast cancer

cells by inducing autophagy in MDA-MB-231 triple-negative and MCF-7 cells and by inhibiting cyclin-dependent kinases p21/CDKN1A (De Santi et al. 2011). 3,3′-Diindolylmethane (DIM) is the digestion product of I3C and is formed in the acidic environment of the stomach. A study showed that DIM induced apoptosis and inhibited the colorectal cancer cells proliferation by targeting the mouse double minute 2 homolog (MDM2), which negatively regulates the tumor suppressor gene p53. A study performed on breast cancer patients with BRCA mutation showed the ability of DIM to reduce the average score of the fibroglandular tissue as revealed by MRI compared with the untreated women (Yerushalmi et al. 2020).

Diallyl-Disulfide and Thiosulfinates

Diallyl disulfide and thiosulfinates (Fig. 5) are sulfur-containing phytochemicals commonly present in garlic – specifically in its volatile oil – and some plants belonging to genus *Allium* with reported anticarcinogenic effect. Thiosulfinate-enriched garlic extract reduced the viability of colorectal cancer cells HT-29 and Caco2 *in vitro*. When combined with fluorouracil or oxaliplatin, it reduced the doses of the chemotherapy and improved the clinical outcomes. The combined diallyl trisulfide/doxorubicin was more efficient in suppressing tumor growth and shrinking tumor volume compared with doxorubicin alone in breast cancer rat model (Elsherbiny et al. 2020). Another organosulfur compound present in fresh garlic is the *S*-allylcysteine (Fig. 5), which displayed anticancer effects by induction of apoptosis and prevention of epithelial–mesenchymal transition and invasion of cancer cells. Synergistic antiapoptotic effect against ER^- breast cancer cells was achieved when *S*-allylcysteine was combined with selenium (Zhang et al. 2020b).

Carotenoids

Carotenoids are tetraterpene pigments with orange, red, and yellow color. They are produced by fungi, bacteria, and plants to absorb the light needed for the photosynthesis. It has been scientifically known that carotenoids showed anticarcinogenic effects against different types of tumors. Crocin and crocetin (Fig. 6) are carotenoids present in saffron, and they exhibited a potent radical scavenging power. They inhibited superoxide dismutase formation in MCF-7 breast cancer cells *in vitro* and *in vivo*

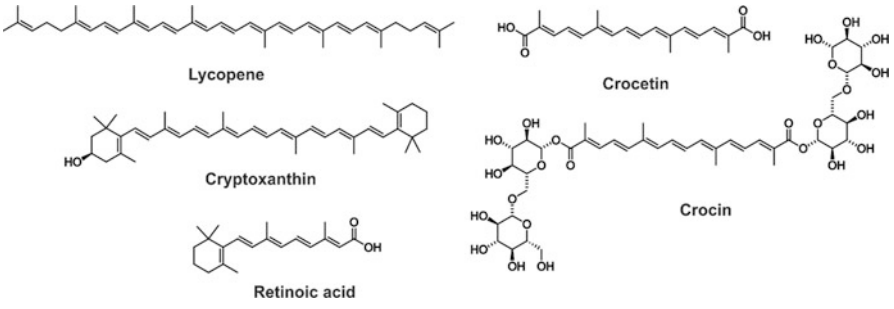

Fig. 6 Carotenoids with cytotoxic activities

(Hashemi et al. 2020). Adiposity and obesity contribute to the poor outcomes for patients with breast cancer. A study showed an inverse association between basal skin carotenoids and adiposity in breast cancer survivors. Lycopene, retinoic acid, and *β*-cryptoxanthin increased the expression of oxoguanine glycosylase-1 (OGG1) gene in doses ranging between 10 and 100 nM therefore decreasing genotoxicity and promoting DNA repair and gene stability in patients with lung cancer (Cheng et al. 2020).

Resveratrol

Resveratrol is a trihydroxy stilbene naturally found in berries and grapes. The peptide–sucrose liposomal formulation of resveratrol exhibited significant inhibition of the growth of MCF-7 breast cancer cells *in vitro* (IC_{50} value of 20.8 μmol/L) and *in vivo* by upregulating the tumor suppressor gene *p53* and the *Bax* gene hence inducing apoptosis (Zhao et al. 2020b). Similar to its efficacy on breast cancer, resveratrol (alone or as a nano formula) significantly reduced the angiogenesis and the vascularity in both the xenograft and the mice model with colorectal carcinoma resulting in the shrinkage of the tumor mass. Resveratrol can sensitize the colorectal cancer cells to cetuximab therapy through the upregulation of connexin 43, which inhibited the downstream PI3K/Akt signaling pathway (Wang et al. 2020b). The cytotoxic activity of resveratrol against non-small-cell lung cancer (NSCLC) was enhanced when formulated as an inhalation in cyclodextrin, hence increasing its aqueous solubility and bioavailability (Wang et al. 2020a). Furthermore, resveratrol is reported as a promising compound for the prevention and treatment of colorectal cancer. It suppressed colorectal cancer cells, by inhibiting both TNF-*α* and TNF-*β*, through the upregulation of apoptotic factors like cleaved caspase-3. In addition, resveratrol inhibited NF-κB activation, gene products of NF-κB-dependent carcinogenic MMP-9 and CXCR4, and EMT-related signaling factors in colorectal cancer cells. Moreover, resveratrol suppressed MMP-9 and vascular endothelial growth factor (VEGF) signaling pathways, thus preventing metastasis and angiogenesis. Due to the significant anticancer effect of resveratrol, many synthetic analogs were developed to enhance its bioavailability by replacing the hydroxy and methoxy groups in resveratrol with heterocyclic rings (Yang et al. 2020).

Curcumin

Curcumin is a diaryl heptanoid and is the main active constituent of turmeric (*Curcuma longa*). Several studies showed its beneficial uses against cancer through its immunomodulatory effects and its ability to trigger the innate immune system to fight cancer (Mukherjee et al. 2020). One study by Eskiler et al. showed that curcumin induced dsDNA breaks in the BRCA1-mutant HCC1937 breast cancer cells; therefore, it could be of therapeutic use for patients with triple-negative breast cancer associated with a mutation in *BRCA-1* gene (Guney Eskiler et al. 2020). However, the anticancer effect of curcumin is limited by its poor bioavailability *in vivo*, for that many methodologies were reported to overcome this problem. A combination of curcumin and piperine (alkaloid present in black pepper) in the form of emulsome nanoformulation was found to have a collaborative effect *in vitro* against HCT116 colorectal cancer cells through the induction of apoptotic cell death and cell cycle arrest.

The delivery of methotrexate to breast cancer cells was successfully achieved in the form of dextran-curcumin nanoparticles (Curcio et al. 2020) even resistance to doxorubicin in triple-negative breast cancer cells was bypassed if formulated in solid lipid nanoparticles loaded with curcumin (Fathy Abd-Ellatef et al. 2020). Applying electrical pulses improved the anticarcinogenic effects of curcumin against MDA-MB-231 triple-negative breast cancer cells by induction of apoptosis, downregulation of 8 key glycolysis proteins and 11 adhesion proteins (Mittal et al. 2020).

Cancer and Diet

Literature in the last decades indicated that food does not only provide energy to living organisms but also has a critical role in regulating genes, protecting the body from internal and external distresses, and influencing the immune system. As it was quoted by Hippocrates "Let the food be thy medicine and thy medicine be thy food," a strong connection lies between food and human health. Thus, nutraceuticals may be used in combination with pharmaceuticals to achieve a synergistic or antagonistic effect that supports cancer prevention (Kerschbaum and Nüssler 2019).

Molecular Biology Effects

Molecular biology effects of some dietary nutraceuticals as anticancer can be exemplified in many examples such as *Allium sativum*, Liliaceae (Garlic) containing *S*-allylcysteine that suppresses the growth of tumors in several animal models (Thomson and Ali 2003). Carnosol in *Rosmarinus officinalis*, Lamiaceae (rosemary) downregulated c-Jun and NF-κB and inhibited the attack of mouse melanoma cells B16/F10; consequently, curping the effect of metalloproteinase-9 (Huang et al. 2005).

Glycine max, Fabaceae (Soybeans) contains the isoflavonoid genistein which down-regulated the MDM2 oncogene at the stages of transcription and post-translation in various human cell lines, for instance, colon, prostate, fibroblast, and breast (Li et al. 2005). 6-Dehydrogingerdione in *Zingiber officinale* tuber, Zingiberaceae (Mostafa 2018) induced cell-cycle arrest, and apoptotic alterations in human breast cancer MCF-7 with MDA-MB-231 with increased levels of p21 and reduced amounts of cyclins (Hsu et al. 2010). Lycopene in *Lycopersicon esculentum*, Solanaceae (tomato) inhibited the activated protein kinases (p38), JNK pathway, and inhibited NF-κB (Kim et al. 2004).

Piperine in *Piper nigrum*, Piperaceae (Black pepper) demonstrated cytotoxicity against DLA and EAC at 250 μg/mL, and against culture cells L929 at 100 and 50 μg/mL, respectively (Sunila and Kuttan 2004). *Piper longum* extract given at 10 mg per animal and piperine given at 1.14 mg per animal both inhibited solid tumor development in mice induced by DLA with significant life span enhancement in mice-bearing tumors of Ehrlich ascites carcinoma with 37.3% and 58.8%, respectively. Furthermore, white blood cells in Balb/c mice were raised to 142.8% and 138.9%, respectively (Sunila and Kuttan 2004).

Ocimum sanctum, Lamiaceae (Basil) contains ursolic acid that inhibited NF-κB activation induced by carcinogenic agents, and downregulated cyclooxygenase-2 enzyme, matrix metalloproteinase 9, and cyclin D1 (Shishodia et al. 2003). Silybin in the milk thistle Silymarin (*Silymarin marianum*, Asteraceae) suppressed different cell proliferations in breast, prostate, lung, bladder, colon, and ovary through G1/S cell cycle arrest, inducing cyclin-dependent kinases acting as inhibitors. Additionally, silybin contributed to AKT cell-survival kinases and NF-κB inhibition. Silymarin downregulates TGF-beta, COX-2, IGF-IR, and EGFR genes responsible for cellular proliferation. Silymarin subdue MMP-9, angiogenesis as via VEGF as well as metastasis mediated by adhesion molecules (Agarwal et al. 2006).

Honey with higher phenolic content 25% v/v i.p. significantly inhibited the growth of Ehrlich ascites carcinoma, gave maximum tumor growth inhibition 39.98%, but less efficacy was shown against Ehrlich solid carcinoma growth (Jaganathan et al. 2010). Eugenol in honey at 100 mg/kg i.p. revealed 28.88% suppression of Ehrlich ascites growth and inhibited solid tumor growth carcinoma by 24.35% (Jaganathan et al. 2010). Capsaicin in *Capsicum annum; Capsicum frutens,* Solanaceae (red chilli) suppressed NF-κB transcription in mouse epidermis (Han et al. 2001). Many essential oils isolated from edible plants showed *in vitro* cytotoxic activities with various mechanisms (Ibrahim and Moussa 2020; Ayoub et al. 2010; Ashmawy et al. 2019; Todirascu-Ciornea et al. 2019). Lemon oil's effect against breast cancer *in vitro* manifested an elevation in expression of caspase-8, together with a reduction in the antiapoptotic protein BcL-2 expression levels and a decrease in the proliferative marker Ki-67 (Ashmawy et al. 2019). *Daucus carota* spp. *carota*, Umbelliferae (wild carrot) contains *β*-carotene. The essential oil significantly raised cell death and diminished cellular proliferation in human colon and breast cancer cell lines (Cheng et al. 2001).

Cucurbitacin E from *Curcurbita moschata*, Cucurbitaceae (Pumpkin) suppressed the expression of VEGF/VEGFR2, Bcl-xl, and cyclin D1. Cucurbitacin E significantly inhibited angiogenesis-activated caspase-3 and induced apoptosis. Cucurbitacin E suppressed phosphorylation of p38 that showed anti-proliferating effect. In prostate carcinoma, it induced cell growth inhibition and inhibited the depolymerization of actin (Colagar and Souraki 2012; Moussa et al. 2020).

The molecular biology effects of curcumin in *Curcuma domestica*, Zingiberaceae (turmeric); epigallocatechin gallate in *Camellia sinensis* (black and green tea), family Theaceae, and resveratrol from *Vitis vinifera* (grapes), family Vitaceae have been discussed earlier. The use of natural compounds or supplements, particularly the edible, treatment might replace current therapeutic strategies (Orlikova et al. 2011; Mostafa et al. 2018). Xanthohumol from *Humulus lupulus*, Cannabiaceae (Hops) and isoliquiritigenin from *Glycyrrhiza glabra*, Leguminosae (Liquorice root) are just a few examples of chalcone containing plants that showed efficacy in several steps of carcinogenesis rather than being linked to specific target. Nevertheless, these compounds could still affect one modulatory protein selectively in signaling pathways, originating a cascade of cellular events that leads to the desired effects (Orlikova et al. 2011). It is worth mentioning that structure–activity relationship studies that explain anticancer activities are in demand more than any time before to highlight the

underlying mechanisms and even develop a roadmap for the production of semi-synthetic molecules facilitating future potential drugs (Elkhawas et al. 2020).

Both Xanthohumol from *Humulus lupulus*, and isoliquiritigenin from *Glycyrrhiza glabra* acted on multiple pathways of inflammation, cell death inducers, inhibitors of cell cycle and revealed effects on steps of tumor initiation, promotion, and progression. Moreover, they inhibited invasion, angiogenesis, and metastasis (Orlikova et al. 2011) (Fig. 7).

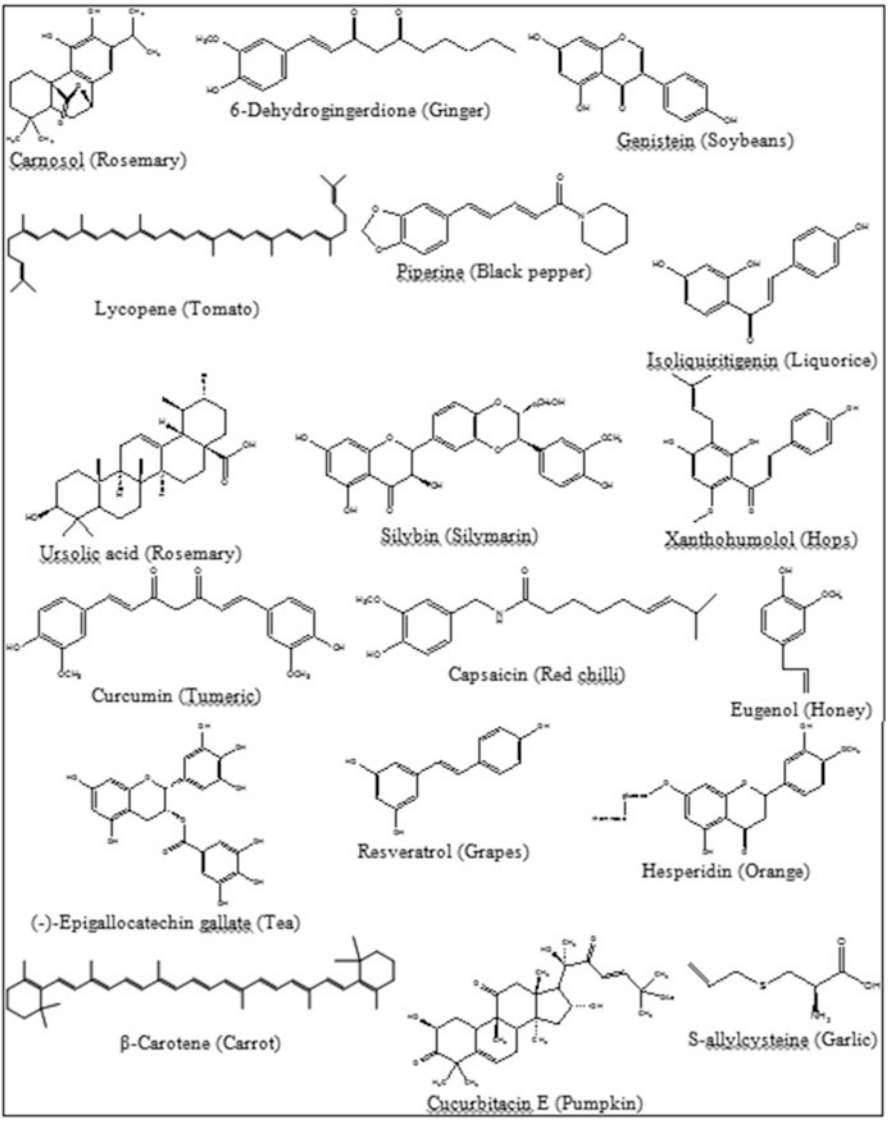

Fig. 7 Representative examples of some anticancer nutraceuticals

Effect of Nutritional Support on Cancer Patients

The clinical use of nutritional support in cancer patients dates to 1913 when Payton Rous first suggested that restricted food intake reduces tumor growth by decreasing the tumor blood supply. The primary attempt to modulate cancer patients' diet was to reduce its carbohydrate content based on the proved concept that cancer cells need large amounts of glucose to survive, and their Krebs cycle enzymes are mutated in various cancer types. Hence, cutting down carbohydrate-rich diet was aimed for by following a calorie restriction protocol with the disseminated crude concept that tumor proliferation could be suppressed by depriving the cells of their major nutrients. Multiple studies recorded that a 30–40% caloric intake restriction alone significantly limited tumor growth. The underlying mechanism behind tumor growth reduction was postulated to be through the alteration of angiogenesis, induction of cancer cell death, and the diminution of both insulin-like growth factor 1 (IGF-1) and insulin (Lv et al. 2014).

Despite the promising results shown with calorie restriction in several cancer models, the therapeutic application in cancer patients is not always successful as anticipated especially over long periods of fasting. One reason is based on the fact that human cells can survive utilizing stored fats. Besides, calorie restriction is contraindicated for underweight and cachexic patients (Nogueira et al. 2012).

Amino acids are engaged in various metabolic pathways to maintain major biosynthetic processes. Hence, protein-targeted diets are another type of diet that can help cancer patients based on patient deprivation of specific amino acid(s) targeting the inhibition of tumor growth. Diets deprived of either methionine, or serine and glycine were executed in different animal models and demonstrated success. However, clinical studies implementing protein-targeted diets experienced various problems. The inefficiency of amino-acid restriction in affecting tumor metabolism was evidenced in clinical studies other than animal models. Besides, avoiding food containing certain amino acid (s) was very challenging (Sinha et al. 2014).

Fatty acids are also involved in cancer development through various aspects that are still under investigation. Beyond being building blocks of biological lipid membranes required by the rapidly dividing cancer cells, they serve as energy reservoirs. Fatty acids via the production of signaling molecules like sphingolipids, phosphoinositides, and eico- and docosanoids assist in cancer growth and expansion. Moreover, increased lipid uptake often leads to lipid droplet appearance storing excess cholesterol and fatty acids that can supply cancer cells with energy upon lipolysis. Accordingly, distant metastasis and cancer local invasiveness were evidenced to be reduced on inhibiting fatty acid mobilization from lipid droplets. The fatty acid synthesis pathway controlled by the transcription factors called sterol-regulatory element-binding proteins (SREBPs) was reported to be stimulated, and the overexpression of SREBPs was evidenced in different cancer types (Corbet et al. 2020).

A high-fat diet is always linked to the progress of different pathologies including cancer. It was reported that a high-fat diet enhanced colon, breast, and pancreatic cancer progression in different animal models. Induction of cancer development

through fatty acid metabolism stimulation and the establishment of an inflammatory environment are the plausible underlying mechanisms (Sundaram and Yan 2016).

PUFAs were recommended as an adjuvant to anticancer therapies, enhancing the efficacy of chemotherapeutic agents and radiotherapy in many animal models. However, clinical studies did not provide sufficient evidence of the efficiency of n-3 PUFAs in cancer therapies (Yam and Shinitzky 2001).

Being involved in the free radical generation and cellular damage, some cytotoxic agents pose dangerous effects on the human body, which were shown to be antagonized by nutraceuticals. An example would be garlic, ginger, and ginkgo supplements whose suppression of cytochrome P450E1 potentiates the level of several drugs in the blood (Calvani et al. 2020).

Vitamin A supplement was taken during the clinical trials of 100 patients suffering from breast cancer and resulted in improved response to cyclophosphamide or doxorubicin (Jaganathan et al. 2010). When decitabine was introduced to the NB4 and HL60 cell lines with low doses of vitamin C, a synergistic effect was noticed in proliferation and apoptosis. This was not only in the *in vitro* assay but also clinical studies evaluating the safety and demonstrated that the combined regimen of decitabine and vitamin C caused higher remission rates in patients than those receiving only decitabine (Allegri et al. 2018). Vitamin D at a dose of 10,000 IU/week was the reason behind the enhanced survival rate of BC patients when combined with antiproliferative drugs (Zeichner et al. 2015).

Nutraceuticals: Challenges and Perspectives

There are many challenges against the formulation of nutraceuticals that hinder their use for medicinal and therapeutic purposes (Siddiqui and Moghadasian 2020). Among them are the following:

- *Contamination*: Nutraceuticals are often not prepared under strict GMP standards due to the absence of authorized control on their production. Commonly detected contaminants are heavy metals, toxins, pesticides, and microbes.
- *Lack of standardization*: The presence of several varieties of the same plant leads to different concentrations of the active ingredient, which could be due to seasonal and/or geographical reasons.
- *Complexity of herbal extracts*: Unlike the synthetic drugs, herbal extracts are highly complicated mixtures of phytochemicals leading to potential herbal–drug interactions.
- *Lack of trustworthy scientific data*: Most nutraceuticals and dietary products are not approved due to the lack of experimental and detailed clinical trials.
- *Formulation problems*: It is quite challenging to formulate nutraceuticals in the proper dosage form due to their low bioavailability, reduced stability, and fast metabolism.

Conclusion

Dietary and herbs-derived nutraceuticals could be of high value for the preventive treatment and/or supportive management of cancer. They act by protecting the cells from the damaging effects of free radicals, hence reducing the possibility of mutagenesis. Additionally, they induce apoptosis and cell cycle arrest in cancer cells. They likewise interfere with the different inflammatory signaling pathways; hence suppressing the progression of cancer.

References

Agarwal R, Agarwal C, Ichikawa H, Singh RP, Aggarwal BB (2006) Anticancer potential of silymarin: from bench to bed side. Anticancer Res 26(6B):4457–4498

Allegri L, Rosignolo F, Mio C, Filetti S, Baldan F, Damante G (2018) Effects of nutraceuticals on anaplastic thyroid cancer cells. J Cancer Res Clin Oncol 144(2):285–294

Almatroodi SA, Almatroudi A, Khan AA, Alhumaydhi FA, Alsahli MA, Rahmani AH (2020) Potential therapeutic targets of epigallocatechin gallate (EGCG), the most abundant catechin in green tea, and its role in the therapy of various types of cancer. Molecules 25(14):3146

Ashmawy A, Mostafa N, Eldahshan O (2019) GC/MS analysis and molecular profiling of lemon volatile oil against breast cancer. J Essential Oil Bearing Plants 22(4):903–916

Ayoub N, Singab AN, Mostafa N, Schultze W (2010) Volatile constituents of leaves of Ficus carica Linn. grown in Egypt. J Essential Oil Bearing Plants 13(3):316–321

Calcabrini C, Maffei F, Turrini E, Fimognari C (2020) Sulforaphane potentiates anticancer effects of doxorubicin and cisplatin and mitigates their toxic effects. Front Pharmacol 11(567). https://doi.org/10.3389/fphar.2020.00567

Calvani M, Pasha A, Favre C (2020) Nutraceutical boom in cancer: inside the labyrinth of reactive oxygen species. Int J Mol Sci 21(6):1936

Chattopadhyay S, Bhattacharyya S, Saha B, Chakraborty J, Mohanty S, Sakib Hossain DM, Banerjee S, Das K, Sa G, Das T (2009) Tumor-shed PGE(2) impairs IL2Rgammac-signaling to inhibit CD4 T cell survival: regulation by theaflavins. PLoS One 4(10):e7382–e7382. https://doi.org/10.1371/journal.pone.0007382

Chen ZP, Schell JB, Ho C-T, Chen KY (1998) Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Cancer Lett 129(2):173–179. https://doi.org/10.1016/S0304-3835(98)00108-6

Cheng J, Miller B, Eroglu A (2020) The efficacy of carotenoids in DNA repair in lung cancer. Curr Dev Nutr 4(Supp 2):99. https://doi.org/10.1093/cdn/nzaa041_003

Cheng Y-H, Shen T-F, Pang VF, Chen B-J (2001) Effects of aflatoxin and carotenoids on growth performance and immune response in mule ducklings. Comp Biochem Physiol C Toxicol Pharmacol 128(1):19–26

Chiaino E, Micucci M, Durante M, Budriesi R, Gotti R, Marzetti C, Chiarini A, Frosini M (2020) Apoptotic-induced effects of Acacia Catechu Willd extract in human colon cancer cells Int J Mol Sci 21 (6):2102. https://doi.org/10.3390/ijms21062102

Colagar AH, Souraki OA (2012) Review of pumpkin anticancer effects. Quran Med 1(4):77–88

Corbet C, Bastien E, de Jesus JPS, Dierge E, Martherus R, Vander Linden C, Doix B, Degavre C, Guilbaud C, Petit L (2020) TGFβ2-induced formation of lipid droplets supports acidosis-driven EMT and the metastatic spreading of cancer cells. Nat Commun 11(1):1–15

Curcio M, Cirillo G, Tucci P, Farfalla A, Bevacqua E, Vittorio O, Iemma F, Nicoletta FP (2020) Dextran-curcumin nanoparticles as a methotrexate delivery vehicle: a step forward in breast cancer combination therapy. Pharmaceuticals 13(1). https://doi.org/10.3390/ph13010002

De Santi M, Galluzzi L, Lucarini S, Paoletti MF, Fraternale A, Duranti A, De Marco C, Fanelli M, Zaffaroni N, Brandi G, Magnani M (2011) The indole-3-carbinol cyclic tetrameric derivative CTet inhibits cell proliferation via overexpression of p21/CDKN1A in both estrogen receptor-positive and triple-negative breast cancer cell lines. Breast Cancer Res 13(2):R33. https://doi.org/10.1186/bcr2855

Dong Z, Ma W-y, Huang C, Yang CS (1997) Inhibition of tumor promoter-induced activator protein 1 activation and cell transformation by tea polyphenols, (-)-epigallocatechin gallate, and theaflavins. Cancer Res 57(19):4414

Elkhawas YA, Elissawy AM, Elnaggar MS, Mostafa NM, Al-Sayed E, Bishr MM, Singab ANB, Salama OM (2020) Chemical diversity in species belonging to soft coral genus Sacrophyton and its impact on biological activity: a review. Marine drugs 18(1):41

Elsherbiny NM, El-Sherbiny M, Zaitone SA (2020) Diallyl trisulfide potentiates chemotherapeutic efficacy of doxorubicin in experimentally induced mammary carcinoma: role of Notch signaling. Pathol Res Pract 216(10):153139. https://doi.org/10.1016/j.prp.2020.153139

Fathy Abd-Ellatef G-E, Gazzano E, Chirio D, Ragab Hamed A, Belisario DC, Zuddas C, Peira E, Rolando B, Kopecka J, Assem Said Marie M, Sapino S, Ramadan Fahmy S, Gallarate M, Zaki Abdel-Hamid A-H, Riganti C (2020) Curcumin-loaded solid lipid nanoparticles bypass P-glycoprotein mediated doxorubicin resistance in triple negative breast cancer cells. Pharmaceutics 12(2). https://doi.org/10.3390/pharmaceutics12020096

Feng X-L, Zhan X-X, Zuo L-S-Y, Mo X-F, Zhang X, Liu K-Y, Li L, Zhang C-X (2020) Associations between serum concentration of flavonoids and breast cancer risk among Chinese women. Eur J Nutr. https://doi.org/10.1007/s00394-020-02331-z

Gosslau A, Chen KY (2004) Nutraceuticals, apoptosis, and disease prevention. Nutrition 20(1): 95–102. https://doi.org/10.1016/j.nut.2003.09.017

Guney Eskiler G, Sahin E, Deveci Ozkan A, Cilingir Kaya OT, Kaleli S (2020) Curcumin induces DNA damage by mediating homologous recombination mechanism in triple negative breast cancer. Nutr Cancer 72(6):1057–1066. https://doi.org/10.1080/01635581.2019.1670216

Han L, Fang S, Li G, Wang M, Yu R (2020) Total flavonoids suppress lung cancer growth via the COX-2-mediated Wnt/β-catenin signaling pathway. Oncol Lett 19(3):1824–1830. https://doi.org/10.3892/ol.2020.11271

Han SS, Keum Y-S, Seo H-J, Chun K-S, Lee SS, Surh Y-J (2001) Capsaicin suppresses phorbol ester-induced activation of NF-κB/Rel and AP-1 transcription factors in mouse epidermis. Cancer Lett 164(2):119–126

Hao Q, Wang M, Sun NX, Zhu C, Lin YM, Li C, Liu F, Zhu WW (2020) Sulforaphane suppresses carcinogenesis of colorectal cancer through the ERK/Nrf2-UDP glucuronosyltransferase 1A metabolic axis activation. Oncol Rep 43(4):1067–1080. https://doi.org/10.3892/or.2020.7495

Hashemi SA, Karami M, Bathaie SZ (2020) Saffron carotenoids change the superoxide dismutase activity in breast cancer: in vitro, in vivo and in silico studies. Int J Biol Macromol 158:845–853. https://doi.org/10.1016/j.ijbiomac.2020.04.063

Hsu YL, Chen CY, Hou MF, Tsai EM, Jong YJ, Hung CH, Kuo PL (2010) 6-Dehydrogingerdione, an active constituent of dietary ginger, induces cell cycle arrest and apoptosis through reactive oxygen species/c-Jun N-terminal kinase pathways in human breast cancer cells. Mol Nutr Food Res 54(9):1307–1317

Huang S-C, Ho C-T, Lin-Shiau S-Y, Lin J-K (2005) Carnosol inhibits the invasion of B16/F10 mouse melanoma cells by suppressing metalloproteinase-9 through down-regulating nuclear factor-kappaB and c-Jun. Biochem Pharmacol 69(2):221–232

Ibrahim N, Moussa AY (2020) Comparative metabolite profiling of Callistemon macropunctatus and Callistemon subulatus volatiles from different geographical origins. Ind Crop Prod. https://doi.org/10.1016/j.indcrop.2020.112222

Jaganathan SK, Mondhe D, Wani Z, Pal HC, Mandal M (2010) Effect of honey and eugenol on Ehrlich ascites and solid carcinoma. J Biomed Biotechnol 2010

Johnson JJ, Bailey HH, Mukhtar H (2010) Green tea polyphenols for prostate cancer chemoprevention: a translational perspective. Phytomedicine 17(1):3–13. https://doi.org/10.1016/j.phymed.2009.09.011

Kerschbaum E, Nüssler V (2019) Cancer prevention with nutrition and lifestyle. Visceral Med 35(4):204–209

Keshandehghan A, Nikkhah S, Tahermansouri H, Heidari-Keshel S, Gardaneh M (2020) Co-treatment with sulforaphane and nano-metformin molecules accelerates apoptosis in HER2+ breast cancer cells by inhibiting key molecules. Nutr Cancer 72(5):835–848. https://doi.org/10.1080/01635581.2019.1655073

Kim GY, Kim JH, Ahn SC, Lee HJ, Moon DO, Lee CM, Park YM (2004) Lycopene suppresses the lipopolysaccharide-induced phenotypic and functional maturation of murine dendritic cells through inhibition of mitogen-activated protein kinases and nuclear factor-κB. Immunology 113(2):203–211

Le Marchand LC, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN (2000) Intake of flavonoids and lung cancer. JNCI: J Natl Cancer Inst 92(2):154–160. https://doi.org/10.1093/jnci/92.2.154

Leu Y-L, Wang T-H, Wu C-C, Huang K-Y, Jiang Y-W, Hsu Y-C, Chen C-Y (2020) Hydroxygenkwanin suppresses non-small cell lung cancer progression by enhancing EGFR degradation. Molecules 25(4). https://doi.org/10.3390/molecules25040941

Li M, Zhang Z, Hill DL, Chen X, Wang H, Zhang R (2005) Genistein, a dietary isoflavone, down-regulates the MDM2 oncogene at both transcriptional and posttranslational levels. Cancer Res 65(18):8200–8208

Li Y, Shi J, Sun X, Li Y, Duan Y, Yao H (2020) Theaflavic acid from black tea protects PC12 cells against ROS-mediated mitochondrial apoptosis induced by OGD/R via activating Nrf2/ARE signaling pathway. J Nat Med 74(1):238–246. https://doi.org/10.1007/s11418-019-01333-4

Liu F, Lv R-B, Liu Y, Hao Q, Liu S-J, Zheng Y-Y, Li C, Zhu C, Wang M (2020) Salinomycin and sulforaphane exerted synergistic antiproliferative and proapoptotic effects on colorectal cancer cells by inhibiting the PI3K/Akt signaling pathway in vitro and in vivo. OncoTargets Therapy 13:4957–4969. https://doi.org/10.2147/OTT.S246706

Lv M, Zhu X, Wang H, Wang F, Guan W (2014) Roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models: a systematic review and meta-analysis. PLoS One 9(12):e115147

Mahadeo A (2020) Effect of exposure to Epigallocatechin gallate-3-gallate and Epicatechin in the proliferation in the Breast Cancer cell line MDA-MB 468. FASEB J 34(S1):1–1. https://doi.org/10.1096/fasebj.2020.34.s1.03744

Meeran SM, Mantena SK, Elmets CA, Katiyar SK (2006) (-)-Epigallocatechin-3-gallate prevents photocarcinogenesis in mice through interleukin-12-dependent DNA repair. Cancer Res 66(10):5512–5520. https://doi.org/10.1158/0008-5472.can-06-0218

Mittal L, Aryal UK, Camarillo IG, Raman V, Sundararajan R (2020) Effective electrochemotherapy with curcumin in MDA-MB-231-human, triple negative breast cancer cells: a global proteomics study. Bioelectrochemistry 131:107350. https://doi.org/10.1016/j.bioelechem.2019.107350

Mostafa NM (2018) Antibacterial activity of ginger (Zingiber officinale) leaves essential oil nanoemulsion against the cariogenic Streptococcus mutans. J Appl Pharm Sci 8(09):034–041

Mostafa NM, Abd El-Ghffar EA, Hegazy HG, Eldahshan OA (2018) New methoxyflavone from Casimiroa sapota and the biological activities of its leaves extract against lead acetate induced hepatotoxicity in rats. Chem Biodivers 15(4):e1700528

Moussa AY, Lambert C, Stradal TEB, Ashrafi S, Maier W, Stadler M, Helaly S (2020) New peptaibiotics and cyclodepsipeptide from Ijuhya vitellina: isolation, identification, cytotoxic and nematicidal activities. Antibiotics-Basel. https://doi.org/10.3390/antibiotics9030132

Mukherjee S, Baidoo JNE, Fried A, Banerjee P (2020) Using curcumin to turn the innate immune system against cancer. Biochem Pharmacol 176:113824. https://doi.org/10.1016/j.bcp.2020.113824

Nogueira LM, Lavigne JA, Chandramouli GV, Lui H, Barrett JC, Hursting SD (2012) Dose-dependent effects of calorie restriction on gene expression, metabolism, and tumor progression are partially mediated by insulin-like growth factor-1. Cancer Med 1(2):275–288

Nouriemamzaden F, Word B, Cotton E, Hawkins A, Littlejohn K, Moore R, Miranda-Carbon G, Orish CN, Lyn-Cook B (2020) Modulation of estrogen α and progesterone receptors in triple

negative breast cancer cell lines: the effects of vorinostat and indole-3-carbinol in vitro. Anticancer Res 40(7):3669–3683. https://doi.org/10.21873/anticanres.14356

Orlikova B, Tasdemir D, Golais F, Dicato M, Diederich M (2011) Dietary chalcones with chemopreventive and chemotherapeutic potential. Genes Nutr 6(2):125–147

Santilli G, Piotrowska I, Cantilena S, Chayka O, D'Alicarnasso M, Morgenstern DA, Himoudi N, Pearson K, Anderson J, Thrasher AJ, Sala A (2013) Polyphenon [corrected] E enhances the antitumor immune response in neuroblastoma by inactivating myeloid suppressor cells. Clin Cancer Res 19(5):1116–1125. https://doi.org/10.1158/1078-0432.ccr-12-2528

Shishodia S, Majumdar S, Banerjee S, Aggarwal BB (2003) Ursolic acid inhibits nuclear factor-κB activation induced by carcinogenic agents through suppression of IκBα kinase and p65 phosphorylation: correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1. Cancer Res 63(15):4375–4383

Sicard A-A, Dao T, Suarez NG, Annabi B (2020) Diet-derived gallated catechins prevent TGF-β-mediated epithelial-mesenchymal transition, cell migration and vasculogenic mimicry in chemosensitive ES-2 ovarian cancer cells. Nutr Cancer:1–12. https://doi.org/10.1080/01635581.2020.1733624

Siddiqui RA, Moghadasian MH (2020) Nutraceuticals and nutrition supplements: challenges and opportunities. Multidisciplinary Digital Publishing Institute

Simões BM, Santiago-Gómez A, Chiodo C, Moreira T, Conole D, Lovell S, Alferez D, Eyre R, Spence K, Sarmiento-Castro A, Kohler B, Morisset L, Lanzino M, Andò S, Marangoni E, Sims AH, Tate EW, Howell SJ, Clarke RB (2020) Targeting STAT3 signaling using stabilised sulforaphane (SFX-01) inhibits endocrine resistant stem-like cells in ER-positive breast cancer. Oncogene 39(25):4896–4908. https://doi.org/10.1038/s41388-020-1335-z

Sinha R, Cooper TK, Rogers CJ, Sinha I, Turbitt WJ, Calcagnotto A, Perrone CE, Richie JP Jr (2014) Dietary methionine restriction inhibits prostatic intraepithelial neoplasia in TRAMP mice. Prostate 74(16):1663–1673

Sundaram S, Yan L (2016) High-fat diet enhances mammary tumorigenesis and pulmonary metastasis and alters inflammatory and angiogenic profiles in MMTV-PyMT mice. Anticancer Res 36(12):6279–6287

Sunila E, Kuttan G (2004) Immunomodulatory and antitumor activity of Piper longum Linn. and piperine. J Ethnopharmacol 90(2–3):339–346

Tao C, Chen J, Huang X, Chen Z, Li X, Li Y, Xu Y, Ma M, Wu Z (2020) CT1-3, a novel magnolol-sulforaphane hybrid suppresses tumorigenesis through inducing mitochondria-mediated apoptosis and inhibiting epithelial mesenchymal transition. Eur J Med Chem 199:112441. https://doi.org/10.1016/j.ejmech.2020.112441

Thomson M, Ali M (2003) Garlic [Allium sativum]: a review of its potential use as an anti-cancer agent. Curr Cancer Drug Targets 3(1):67–81

To D-C, Hoang D-T, Tran M-H, Pham M-Q, Huynh N-T, Nguyen P-H (2020) PTP1B inhibitory flavonoids from Orthosiphon stamineus Benth. and their growth inhibition on human breast cancer cells. Nat Prod Commun 15(1):1934578X19899517. https://doi.org/10.1177/1934578X19899517

Todirascu-Ciornea E, El-Nashar HA, Mostafa NM, Eldahshan OA, Boiangiu RS, Dumitru G, Hritcu L, Singab ANB (2019) Schinus terebinthifolius essential oil attenuates scopolamine-induced memory deficits via cholinergic modulation and antioxidant properties in a zebrafish model. Evid Based Complement Alternat Med 2019

Wang X, Parvathaneni V, Shukla SK, Kulkarni NS, Muth A, Kunda NK, Gupta V (2020a) Inhalable resveratrol-cyclodextrin complex loaded biodegradable nanoparticles for enhanced efficacy against non-small cell lung cancer. Int J Biol Macromol 164:638–650. https://doi.org/10.1016/j.ijbiomac.2020.07.124

Wang Y, Wang W, Wu X, Li C, Huang Y, Zhou H, Cui Y (2020b) Resveratrol sensitizes colorectal cancer cells to cetuximab by connexin 43 upregulation-induced Akt inhibition. Front Oncol 10(383). https://doi.org/10.3389/fonc.2020.00383

Way T-D, Lee H-H, Kao M-C, Lin J-K (2004) Black tea polyphenol theaflavins inhibit aromatase activity and attenuate tamoxifen resistance in HER2/neu-transfected human breast cancer cells through tyrosine kinase suppression. Eur J Cancer 40(14):2165–2174. https://doi.org/10.1016/j.ejca.2004.06.018

Wen S, Sun L, An R, Zhang W, Xiang L, Li Q, Lai X, Huo M, Li D, Sun S (2020) A combination of Citrus reticulata peel and black tea inhibits migration and invasion of liver cancer via PI3K/AKT and MMPs signaling pathway. Mol Biol Rep 47(1):507–519. https://doi.org/10.1007/s11033-019-05157-z

Yam D, Shinitzky M (2001) Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin. Cancer Chemother Pharmacol 47(1):34–40

Yang GY, Liao J, Kim K, Yurkow EJ, Yang CS (1998) Inhibition of growth and induction of apoptosis in human cancer cell lines by tea polyphenols. Carcinogenesis 19(4):611–616. https://doi.org/10.1093/carcin/19.4.611

Yang M-F, Yao X, Chen L-M, Gu J-Y, Yang Z-H, Chen H-F, Zheng X, Zheng Z-T (2020) Synthesis and biological evaluation of resveratrol derivatives with anti-breast cancer activity. Arch Pharm 353(7):2000044. https://doi.org/10.1002/ardp.202000044

Yerushalmi R, Bargil S, Bar Y, Ozlavo R, Tuval S, Rapson Y, Pomerantz A, Zoref D, Sharon E, Caspi O, Grubsrein A, Margel D (2020) 3,3-Diindolylmethane (DIM): a nutritional intervention and its impact on breast density in healthy BRCA carriers. A prospective clinical trial. Carcinogenesis. https://doi.org/10.1093/carcin/bgaa050

Zeichner SB, Koru-Sengul T, Shah N, Liu Q, Markward NJ, Montero AJ, Glück S, Silva O, Ahn ER (2015) Improved clinical outcomes associated with vitamin D supplementation during adjuvant chemotherapy in patients with HER2+ nonmetastatic breast cancer. Clinical Breast Cancer 15(1):e1–e11

Zhang D, Nichols HB, Troester M, Cai J, Bensen JT, Sandler DP (2020a) Tea consumption and breast cancer risk in a cohort of women with family history of breast cancer. Int J Cancer 147(3):876–886. https://doi.org/10.1002/ijc.32824

Zhang W, Tocmo R, Parkin KL (2020b) Synergistic effects of S-alkenylmercaptocysteine (CySSR) species derived from Allium tissue and selenium on inducing apoptosis in ER−breast cancer cells. J Funct Foods 65:103786. https://doi.org/10.1016/j.jff.2020.103786

Zhao C, Ghosh B, Chakraborty T, Roy S (2020a) Bavachinin mitigates DMH induced colon cancer in rats by altering p53/Bcl2/BAX signaling associated with apoptosis. Biotechnic Histochem:1–12. https://doi.org/10.1080/10520295.2020.1778087

Zhao YN, Cao YN, Sun J, Liang Z, Wu Q, Cui SH, Zhi DF, Guo ST, Zhen YH, Zhang SB (2020b) Anti-breast cancer activity of resveratrol encapsulated in liposomes. J Mater Chem B 8(1):27–37. https://doi.org/10.1039/C9TB02051A

Zhu W, Li MC, Wang FR, Mackenzie GG, Oteiza PI (2020) The inhibitory effect of ECG and EGCG dimeric procyanidins on colorectal cancer cells growth is associated with their actions at lipid rafts and the inhibition of the epidermal growth factor receptor signaling. Biochem Pharmacol 175:113923. https://doi.org/10.1016/j.bcp.2020.113923