Plant-Derived Nutraceuticals

Subjects: Oncology

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The term nutraceutical combines the words nutrition and pharmaceutical and indicates those nutrient principles that are found within foods. These have beneficial health effects. Nutraceutical substances derive mainly from plants, food, and microbial sources.

nutraceuticals   gene expression   epigenetic therapy   cancer

1. Curcumin

Curcuma longa L. is an herbaceous plant, perennial and rhizomatous, which belongs to the family of Zingiberaceae, as ginger (*Zingiber officinale* Rosc.) also does. The root, which is the most important component of phytotherapeutic and nutritional interest, is constituted by a cylindrical, branched, aromatic rhizome of orange-yellow color. It is used in food as a spice, especially in traditional Indian, Middle Eastern, and Thai cuisine. The plant contains more than 100 chemical compounds, but the term curcumin generally refers to 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, a compound known as "curcumin I". Two other best-known compounds are curcumin II (demethoxycurcumin, 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione) and curcumin III (bisdemethoxycurcumin, 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione) [1]. The specific and well-known yellow curcumin color is due to "curcumin I" and the curcuminoids, bisdemethoxycurcumin and demethoxycurcumin, generally used as a natural dye in the food industry [2]. The principal essential oils of curcumin are turmerone (ar-turmerone), β-turmerone, α-turmerone, β-bisabolene, β-sesquiphellandrene, α-zingiberene, curcumol, and curcumenol [3].

Curcumin is famous for its antioxidant, anti-inflammatory, and anticancer properties and recently has been shown to act as an epigenetic modulator [4]. The role of curcumin as an epigenetic regulator includes histone modification by the regulation of histone acetyltransferase (HAT) and histone deacetylase (HDAC); DNA methylation by the inhibition of DNA methyltransferase (DNMT); microRNA modulation by the upregulation of tumor-suppressive miRNAs (miR-15a, miR-16, miR-22, miR-26a, miR-34a, miR-145, miR-146a, miR-200b, c, miR-203, and let-7) [5][6]; the downregulation of oncogenic miRNAs (miR-19a, b, miR-21, miR-27a, miR-130a, miR-186) [7]; and the activation of transcription factors, cytokines, and tumor suppressor genes [8]. DNA methylation is a great target in the treatment of acute myeloid leukemia (AML) as it is well known that the inactivation of genes due to DNA methylation has a major role in the development of AML. It has been shown that curcumin is able to downregulate DNMT1 expression in AML cell lines, in vitro and in vivo [9]. p65 and Sp1 expression, positive regulators of DNMT1,

may be reduced by curcumin, which correlates with reductions in the binding of these transcription factors to the DNMT1 promoter in AML cell lines. These characteristics of curcumin make it a promising compound in the treatment of AML [10]. Due to the changes in DNA methylation, curcumin is a hypomethylating agent in breast, prostate, colon, and lung cancer.

Curcumin is able to target other, different cancer-related pathways, such as tumor suppressor genes, growth-signaling factors, transcription factors, apoptotic genes, oncoproteins, the biomarkers of inflammation, or protein kinases [11].

1.1. Anticancer Activity and the Suppression of Carcinogenesis

One of the main mechanisms of the anticancer effects of curcumin is due to its interference in the cell cycle and reduction in cyclin-dependent kinase (CDK) expression that controls cell-cycle progression [12]. Curcumin is able to suppress the human epidermal growth factor receptor 2, a tyrosine kinase (HER2-TK), and in this manner inhibits breast cancer cell lines [13]. By administering curcumin, there is a decrease in the activation of the PI3K (phosphoinositide 3-kinase)/AKT (AKT serine/threonine kinase) signaling pathway, resulting in an anticancer effect via the negative modulation of this cell-signaling pathway [14].

Curcumin can modulate the activity of different transcription factors, inhibiting some of them, such as nuclear factor-κB (NF-κB), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, hypoxia-inducible factor-1 (HIF-1), Notch-1, early growth response-1 (Egr-1), and β-catenin, but activating others, such as NF-E2-related factor (Nrf2) [11][15]. Transcription factors play an important role in various stages of carcinogenesis, being involved in cell proliferation, cell survival, invasion, angiogenesis, and inflammation. Most of these factors are upregulated in most cancers [15]. It has been demonstrated that curcumin inhibits STAT3 phosphorylation, which is responsible for signaling carcinogenic pathways [16]. Furthermore, curcumin is a potent inhibitor of NF-κB, and this effect is correlated with cellular apoptotic response [17]. Likewise, curcumin stimulates the expression of pro-apoptotic Bax and inhibits the activation of Mcl-1 and Bcl-2 (apoptosis regulator) antiapoptotic agents, also altering the expression of apoptotic mechanisms associated with NF-κB proteins, p38 and p53 [18].

1.2. Inhibition of Angiogenesis

In some tumors, curcumin inhibits angiogenesis by suppressing angiogenic cytokines, such as *IL*-6, *IL*-23, and *IL*-1β [19], and it is a direct inhibitor of angiogenesis by downregulating transcription factors, such as NF-κB, and proangiogenesis factors, such as bFGF (basic fibroblast growth factor), VEGF (vascular endothelial growth factor), and MMPs (matrix metalloproteinases), all of them linked with tumorigenesis [20].

1.3. Anti-Inflammatory Properties

Curcumin is a highly pleiotropic molecule, able to interact with numerous molecular targets involved in the inflammatory process, hence the strong anti-inflammatory action both in the acute phase and in the chronic phase

of inflammation. Due to its strong anti-inflammatory effects, in several studies, curcumin showed the ability to prevent the development of some types of cancer by reducing the production of COX-2, lipoxygenase 2, iNOS, and related cytokines, known as mediators of the inflammatory process [21].

Furthermore, curcuminoids are able to exert antioxidant action by blocking free-circulating radicals and inhibiting the formation of new ones [22]. Curcumin can also increase the antioxidant activity, in vitro and in vivo, of the enzymes SOD, CAT, GST, and GSR, and, in this manner, curcumin directly inhibits the formation of reactive species, including superoxide radicals, nitric oxide radicals, and hydrogen peroxide. On the other hand, curcumin also increases the activity of detoxifying enzymes by reducing xenobiotics, therefore protecting against carcinogenic processes [23]. In light of these facts, research is aimed at clarifying the beneficial effects of the combination of curcumin with various antineoplastic drugs so as to improve their clinical effects and reduce their toxicity [13][24].

Although curcumin has significant medicinal properties, its poor bioavailability has limited the success of in vivo epigenetic studies, only partly bypassed by the possibility of using high dosages of the active ingredient in relation to its very low toxicity. Recently, pharmaceutical research has led to the introduction in the market of molecules with better bioavailability (phytosome technology), also opening new therapeutic horizons in terms of preventive medicine and antiaging [25].

In order to overcome the main disadvantages related to the oral administration of curcumin, new strategies for its efficient delivery have been investigated. Among the curcumin formulation strategies used in order to enhance its absorption are lipid additions (such as turmeric oil, piperine, or turmeric oleoresin), the adsorption and dispersion of curcumin onto various matrices (such as γ-cyclodextrin or whey protein), and particle size reduction, but also modified structures of curcumin analogs and micellar and nanoparticle formulations of curcumin [26][27]. Unfortunately, some of these formulations claimed an enhanced bioavailability of curcumin only on the basis of increased solubility, without considering the solubility–permeability interplay in the gastrointestinal tract when using solubility-enabling formulations for oral lipophilic drugs [26][28]. The most important goals in the development of curcumin delivery systems are enhancing solubility, increasing bioavailability by enhancing small intestine permeation, preventing degradation in the intestinal environment, increasing content in the bloodstream, and increasing efficacy. Among the delivery systems that have shown promising results in this regard are micelles, liposomes, phospholipid complexes, nanoemulsions, microemulsions, emulsions, solid lipid nanoparticles, nanostructured lipid carriers, biopolymer nanoparticles, microgels, nanogels, etc. [26][27][29][30][31].

2. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a stilbenoid, a polyphenolic phytoalexin produced by some plants in response to injury or attack by pathogens, such as fungi or bacteria. Sources of resveratrol in food include grapes (*Vitis vinifera* L.), blueberries (*Vaccinium corymbosum* L.), raspberries (*Rubus idaeus* L.), mulberries (*Morus alba* Hort. ex Loudon L.), and peanuts (*Arachis hypogaea* L.). Resveratrol presents two geometric isomers: *cis*-(*Z*) and *trans*-(*E*). The *trans* form exposed to ultraviolet radiation can undergo isomerization to the *cis form* [32].

The *cis* form is dominant in prevalence and especially in= biological activity such as cell-cycle arrest, apoptosis, differentiation, and the anti-proliferation of cancer cells [33][34]. Originally, resveratrol was isolated by Takaoka in 1940, from the roots of white hellebore (*Veratrum album* L.), and in 1963, from knotweed (*Polygonum cuspidatum* Sieb. et Zucc) root. However, only in 1992 did resveratrol attract attention when its presence in wine was associated with the cardioprotective effects of this beverage. *Polygonum cuspidatum* Sieb. et Zucc. is one of the richest sources of resveratrol in nature and, for this reason, it has become a very important plant in modern herbal medicine [35][36].

2.1. Antioxidant and Anti-Inflammatory Activity

Resveratrol is able to exert powerful antioxidant and anti-inflammatory action. As an antioxidant, it has a superior activity to that of more known molecules, such as vitamin C and E, and is also more effective than flavonoids because it also acts upstream of the reaction, rendering copper inactive as a catalyst through its chelation [37].

In addition to the direct antioxidant effect, resveratrol also regulates the gene expression of the prooxidant and antioxidant enzymes: SOD1 and GPX1 are strengthened by resveratrol in a concentration-dependent manner. Therefore, the suppression of the expression of the prooxidant genes (via NADPH-oxidase) and the induction of antioxidant enzymes, such as SOD1 and GPX1, are important components of the antioxidant protective effect induced by resveratrol [38]. Resveratrol has been proven to be an effective scavenger of free radicals, including superoxide radical (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), nitric oxide (NO), and nitrogen dioxide (NO_2) [39][40].

However, direct scavenger activities are relatively scarce, also due to the reduced in vivo half-life of this molecule. The antioxidant properties of resveratrol in vivo, on the other hand, are due to its effect as a regulator of gene expression. Resveratrol induces the downregulation of NADPH-oxidase, with a consequent reduction in reactive oxygen species (ROS). Furthermore, by hyperstimulating tetrahydrobiopterin-GTP-cyclohydrolase, the expression of a variety of antioxidant enzymes is increased. Some of the genes regulating the effect of resveratrol are mediated by Nrf2 [41].

2.2. Resveratrol and Cells Apoptosis

The role of resveratrol as a modulator of cell apoptosis is fundamental. The cellular apoptosis promoted by resveratrol can be mediated by multiple mechanisms, such as the upregulation of cyclin-dependent kinase inhibitors; the activation of mitochondria and cascade of caspases, apoptosis-inducing cytokines, and related receptors; the downregulation of cell survival proteins (e.g., survivin, XIAP (X-linked inhibitor of apoptosis protein), cIAPs, cFLIP, Bcl-XL, Bcl-2); and the inhibition of cell survival kinases (e.g., MAPK, AKT/phosphoinositide 3-kinase (PI3K), PKC, EGFR kinase) and transcription survival factors (e.g., NF-κB, AP-1, HIF-1α, and signal transducer and transcription activator (STAT3)). The induction of one of these pathways by resveratrol leads to cell death [42][43].

Resveratrol regulates proteins involved in DNA and cell-cycle synthesis, such as p53 and Rb/E2F, CDK, and their inhibitors. Resveratrol influences the activity of transcription factors involved in proliferation and stress response, such as NF-κB, AP1, and EGR1. One part of these events is mediated by MAPK and tyrosine kinase, for example, SRC, and leads to the modulation of survival and apoptotic factors (e.g., members of the Bcl-2 family, inhibitors of apoptosis) as well as to the modulation of enzymes involved in carcinogenesis (e.g., cyclooxygenase (COX), nitric oxide synthase (NOS), phase I and II enzymes) [42]. Finally, resveratrol helps regulate the activity and expression of co-transcription factors such as p300 and SIRT1 [44].

Resveratrol also promotes the activation of sirtuins [45] (**Figure 1**) in synergy with melatonin. The fact that melatonin and resveratrol are present in various foods implies possible synergistic effects, suggesting combined use to promote health and longevity [46].
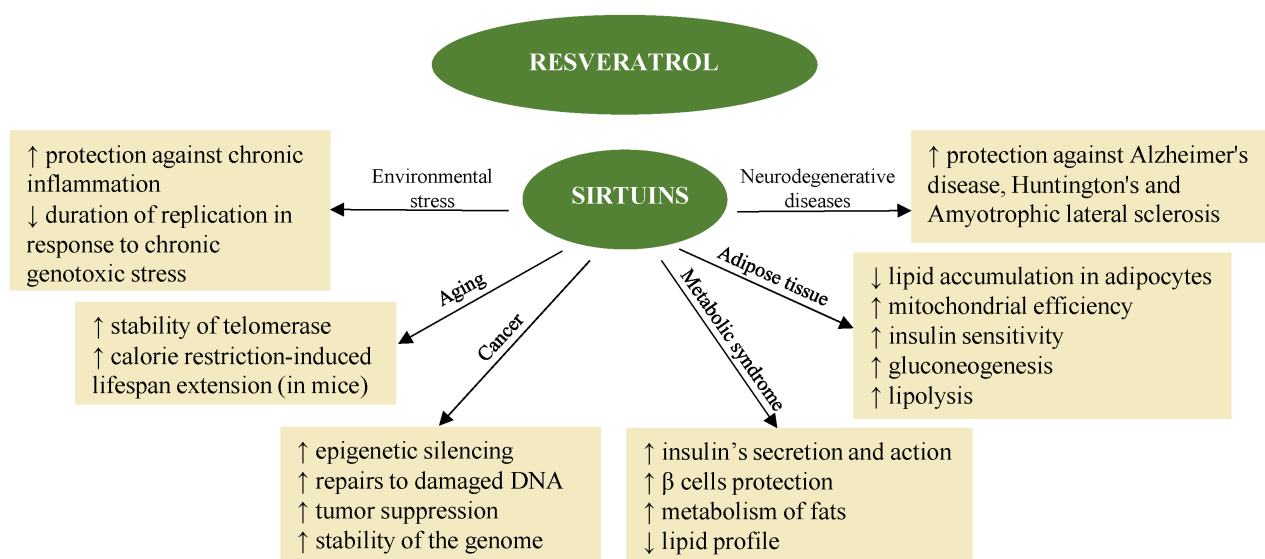

Figure 1. Resveratrol exerts different effects by activating sirtuin [47].

The mechanism of epigenetic action in the case of resveratrol also suggests its indication in the treatment of neurodegenerative diseases [48][49]. In fact, the neuroprotective and neurotrophic effects induced by resveratrol have been the subject of multiple studies, both in vitro and in vivo, and make it again a dietary epidrug in the adjuvant treatment and prevention of these diseases [49]. Resveratrol induces autophagy, directly inhibiting the mTOR pathway through interaction with the ATP-binding pocket of mTOR (it direct competes with ATP) [50]. Likewise, it induces the death of tumor cells, also thanks to the inhibition of the mTORC1 pathway [51].

Resveratrol bioavailability is increased by gastric juices, so it is recommended to take it with meals [52]. In addition, the circadian rhythm and the type of meal may influence bioavailability [53][54]. Therefore, in order to increase the bioavailability of resveratrol, the best time to administer it turned out to be in the morning [54]. There are wide margins of safety and non-toxicity. Lower doses have a beneficial effect, while higher doses (2 g/day or more) can be associated with a number of side effects, such as diarrhea, nausea, abdominal pain, hypersensitivity, or frontal headache [53][55]. The best dose range, for an actual clinical benefit in vivo, is between 250 mg and 500 mg/day [56].

One of the strategies that may improve the pharmacokinetics and bioavailability of resveratrol is the synergism with other phytochemicals, such as piperine. Thus, the co-administration of resveratrol and piperine has improved the bioavailability of resveratrol by inhibiting its rapid metabolism [57][58]. The use of polydatin, a compound that is extracted from the roots of the *Polygonum cuspidatum* Sieb. et Zucc. plant and differs from resveratrol by the presence of one molecule of glucose—which makes the compound more water-soluble and, consequently, more bioavailable than resveratrol—has also been discussed [55]. It has also been considered to increase the bioavailability of orally administrated resveratrol by using alternative routes of administration, such as inhalers and transdermal, buccal, and nasal–brain routes, obtaining promising results [59].

Other measures that may improve the pharmacokinetics of resveratrol, and therefore bioavailability, have focused on innovative delivery systems, such as nanoemulsions, nanosuspensions, dendrimers, liposomes and nanoliposomes, solid lipid nanoparticles, and polymeric nanoparticles [57][58][60].

3. Sulforaphane, Indole-3-Carbinol, and 3,3′-Diindolylmethane

The consumption of cruciferous vegetables, such as broccoli (*Brassica oleracea* var. *italica* Plenck), cabbage (*Brassica oleracea* var. *capitata* L.), brussels sprouts (*Brassica oleracea* var. *gemmifera* Zenker), cauliflower (*Brassica oleracea* var. *botrytis* L.), and kale (*Brassica oleracea* var. *viridis* DC. L.) has been associated with anticancer and antioxidant effects. Considerable evidence shows that glucosinolates (GLSs) are the main phytochemicals in cruciferous vegetables that contribute to their health effects [61]. GLSs are relatively inactive and necessitate hydrolysis by plant endogenous myrosinase (MYR) to deliver a variety of bioactive compounds, such as isothiocyanates (ITCs) and indoles. Neutral pH conditions are favorable for the formation of ITCs [62][63]. GLSs and the enzyme MYR are stored in different compartments of plant cells, requiring plant tissue to be damaged for cellular breakdown to occur and MYR to be released and act on GLSs. Therefore, the processing of cruciferous vegetables (i.e., by mastication, cutting, chopping) has an important impact on the bioavailability of GLSs and their hydrolysis products [64][65].

Concerning the assimilation by the body of the GLS hydrolysis products, absorbed ITCs are conjugated to glutathione, with the involvement of glutathione-S-transferase (GST) enzymes, and metabolized via the mercapturic acid pathway [63]. The polymorphisms of genes coding for GST may have an important effect on ITC metabolism, leading to interindividual variations in the benefits from exposure to these compounds. For instance, individuals carrying deletions in both GST M1 and GST T1 genes may show a more rapid elimination of ITCs, requiring a high intake of cruciferous vegetables in order to capitalize on their positive health effects [66]. As for the metabolism of indoles, molecules such as indole-3-carbinol (I3C) principally undergo oxidative metabolization to indole-3-carboxaldehyde and indole-3-carboxylic acid. The quantification of ITC and indole metabolites in human urine and plasma may serve as an approach to characterize the intake of bioactive compounds from cruciferous vegetables [67][68]. Indeed, it has been demonstrated that the urinary elimination of mercapturic acids after the consumption of cooked cruciferous vegetables accounts for a maximum of 20% of the ingested GLSs. If the vegetables are consumed in the raw form, the rate can reach 88% [62].

To date, the most extensively studied ITCs and indoles are SFN and I3C, respectively. SFN is the precursor of glucoraphanin, the main GLS in broccoli, accounting for about 80% of the total yield [69]. Glucobrassicin is also an important GLS in broccoli [68]. The cleavage of glucobrassicin by MYR generates predominantly I3C. In the acidic conditions at the gastric level, I3C further forms a mixture of dimers, linear and cyclic trimers, and higher oligomers, with 3,3′-diindolylmethane (DIM) being the major condensation product [67][70]. Between 20 and 40% of the ingested I3C is converted to DIM [71]. In fact, several studies have suggested that the health effects of I3C can be mainly attributed to DIM [70][72]. I3C, as well as its acid condensation products, are absorbed at the intestinal level and then distributed into several well-perfused tissues, where they exhibit their biological activities [73].

Currently, SFN, I3C, and DIM are considered promising cancer chemopreventive compounds. I3C is also recognized to have biological properties such as the inhibition of inflammation and angiogenesis, decreases in proliferation, and the promotion of tumor cell death [74].

3.1. Chemopreventive Activity and Epigenetic Role

There is much evidence to connect the chemopreventive properties of I3C, DIM, and SFN with epigenetic mechanisms [75]. Several studies suggest that, at least in part, the chemopreventive effects of I3C are due to the downregulation of class I HDAC isoenzymes (HDAC1, HDAC2, HDAC3, and HDAC8) by DIM. Decreased HDAC expression leads to the increased expression of the pro-apoptotic Bcl-2 (B-cell lymphoma 2)-associated X (Bax) protein, CDKNs p21, and p27 followed by the arrest of the cell cycle and increased rate of apoptosis. For this reason, HDAC inhibition may be a novel epigenetic mechanism for cancer prevention by DIM [76].

SFN may target the aberrant hypermethylation status by downregulating the expression of DNMT1 and DNMT3a in breast cancer cells [77].

Cyclin D2 is a major regulator of the cell cycle and its hypermethylation is correlated with prostate cancer progression. SFN is capable of decreasing the expression of DNMT1 and DNMT3b and epigenetically modulating cyclin D2 expression, acting as a prostate cancer chemopreventive agent [78].

I3C and DIM modulate the expression of several miRNAs and lncRNAs [19][20]. Thus, DIM increases the expression of tumor suppressor microRNAs, such as let-7a-e, miRNA-15a, miRNA-16, miR-27b, miR-30e, miR-31, miR-34a, miR-124, miR 200 a, miR 200b, miR 200c, miR-219-5p, and miR-320, and decreases the expression of oncogenic miR19a, miR19b, miR92a-2, miR 106a, miR 181a, miR 181b, miR 210-3p, miR 221, and miR 495 [71][79][80].

3.2. Effect of Estrogen Analog and Anticarcinogenic in Mammary Tumor Cells

I3C is capable of arresting the growth of human tumor cells in the G1 phase of the reproductive cell cycle [81]. I3C is also a potent inducer of cytochrome P450 enzymes, including CYP1A1, CYP1A2, and CYP1B1 [82][83]. These phase I metabolizing enzymes are involved in the oxidative metabolism of estrogens. I3C and DIM can alter endogenous estrogen metabolism by increasing the 2-hydroxylation reaction, resulting in an increase in the 2-OH:16-OH ratio relative to the estrogen metabolites [84]. The metabolites of these hormones can inhibit or stimulate

the onset of hormone-sensitive neoplasms [85]. Several studies have demonstrated that estrone 2 (2OHE1) tends to inhibit the growth of the neoplasm, whereas estrone 16 (16OHE1) promotes tumor growth [86].

The positive effects of I3C and DIM are related to the fact that both are capable of modifying the estradiol hydroxylation receptor site, resulting in the diminution of 16-α-hydroxyestrone production in favor of 2-hydroxyestrone. I3C and DIM are also involved in the stimulation of liver detoxifying enzyme production, capable of neutralizing and degrading the harmful metabolites of estrogens and xenoestrogens, assimilated as environmental or food pollutants [87][88].

3.3. Anticancer Activity

The SFN also exhibits anticancer action by controlling the progression of tumorigenesis. In non-small cell lung cancer (NSCLC), the SFN is able to attenuate the signaling pathway of EGFR, suggesting an anticancer mechanism of action [89]. As a whole, it has shown multiple effects, including the arrest of cell growth, differentiation, and apoptosis, as recently demonstrated in the case of prostate neoplasms [90].

SFN inhibits the proliferation, in vivo, of breast cancer cells, while in normal cells the effect is insignificant. Cancer cells are characterized by the high expression of telomerase. Treatment with SFN inhibits the catalytic subunit of human telomerase reverse transcriptase (hTERT) [91]. At the same time, scientific studies have shown interference in DNA methyltransferase (DNMT) activity, in particular DNMT1 and DNMT3a, which have been reduced in breast cancer cells treated with SFN, suggesting that this compound may be able to repress hTERT through specific epigenetic pathways. Furthermore, the downregulation of hTERT expression facilitates the induction of cell apoptosis in breast cancer cells, paving the way for approaches aimed at the SFN-mediated prevention of this neoplasia and as preventive nutraceuticals [92].

3.4. Anti-Inflammatory Activity

Inflammation is usually associated with chronic disease and cancer. It is well known that NF-κB is a major transcription factor involved in the regulation of the expression of many pro-inflammatory genes, such as COX-2 and iNOS. I3C and DIM exert anti-inflammatory effects by the downregulation of COX-2, iNOS, CXCL5, and IL-6 expression, which may be mediated by reductions in NF-κB activation [93].

In conclusion, the GLSs present in cruciferous vegetables have beneficial effects on general health and are also potential anticancer agents, due to their antioxidant and detoxifying properties and epigenetic mechanisms, including the modification of CpG (cytosine–phosphate–guanine) methylation, which occurs predominantly in cancer-related genes, the regulation of histone modification, and changes in miRNA expression [94][95].

The daily dosage of SFN demonstrated to provide beneficial health effects is around 20–40 mg [96]. Furthermore, the recommended daily dosage for I3C ranges between 200 mg and 900 mg per day and for DIM between 25 mg and 450 mg per day, respectively. The use over time must include both urinary and blood hormone monitoring, including, in the urine, the observation of the relationship between estrone 2 and estrone 16 and, at the hematic

level, of the total estrone and estradiol and total and free testosterone and androstenedione, so as to constantly adapt the therapy. A diet rich in cruciferous vegetables seems to provide SFN, I3C, and DIM in sufficient amounts for the prevention of many types of cancer, including those that are hormone-related, such as breast, ovary, uterus, and prostate neoplasms [97][98][99]. In contrast, to achieve therapeutic concentrations of SFN, I3C, and DIM, the intake of these compounds in the form of dietary supplements seems to be required [71][100].

The exploitation of SFN by the nutraceutical industry has faced some challenges because this ITC shows high lipophilicity, low aqueous solubility, and poor stability due to sensitivity to oxygen, heat, and alkaline conditions. However, the use of nanotechnology has allowed the increase in the aqueous solubility and bioavailability of SFN through the development of formulations such as polymeric nanoparticles, magnetic nanoparticles, micelles, liposomes, and carbon dots [100].

Likewise, the low thermal- and photostability of I3C and DIM represent important challenges for the nutraceutical application of these compounds. One approach to overcome this issue has been proposed by Luo et al. (2013), who showed that the encapsulation of I3C and DIM in zein/carboxymethyl chitosan nanoparticles can protect these bioactives against temperature- and light-induced degradation [101].

4. Astaxanthin

Astaxanthin (3,3′-dihydroxy-β, β′-carotene-4,4′-dione) (ASX) is a red-orange pigment, a xanthophyll carotenoid, and a member of the macro-family of carotenoids [102]. Synthesized in appropriate quantities by microalgae—*Haematococcus lacustris* (Gir.-Chantr.) Rostaf., *Chromochloris zofingiensis (Donz) Fucikova and L. A. Lewis*, *Chlorococcum sp.*, and *Phaffia rhodozyma* M.W. Mill., Yoney. and Soneda—ASX enters the food chain through crustaceans and predatory fish such as salmon, in whose meat it can easily reach 5–10 mg/kg [103].

ASX has antioxidant potential, as well as anti-inflammatory and antineoplastic activities, acting as an antioxidant and reducing oxidative stress, thereby preventing protein and lipid oxidation and DNA damage. Having antioxidant action, it helps to maintain the functionality of tissues and systems, promoting better overall homeostasis [102].

ASX affects tumor growth in different types of cancers. Several studies have demonstrated that ASX is able to resensitize gemcitabine-resistant human pancreatic cancer cells to gemcitabine [104]. ASX increases DNMT3a expression at low concentrations, but at high concentrations decreases the expression of DNMT1, 3a, and 3b and attenuates NAD(P)H Quinone Dehydrogenase 1 (NQO1) expression via the Nrf2/KEAP1 pathway, reducing cell viability in prostate and skin cancer cells [105][106]. ASX has also the ability to reduce tumor growth in prostate cancer by increasing the expression of tumor suppressor microRNAs, miR-375 and miR-478b [107]. In breast cancer, ASX negatively affects cell viability [108][109], due to apoptotic and autophagic effects that allow it to kill the cancer cells without affecting normal cells [110].

In colorectal cancer (CRC), ASX has demonstrated anti-migratory and anti-invasive activity by increasing miR-29a-3p and miR-200a expression, suppressing MMP2 and ZEB1 expression, resulting in the repression of the

epithelial–mesenchymal transition (EMT) of CRC cells [111]. Regarding lung cancer, NSCLC accounts for the majority of lung cancer-related deaths [112]. There are few studies to show the effects of ASX against NSCLC or other lung cancers in vivo. In vitro, ASX is able to reduce the viability of NSCLC cells in a dose-dependent manner [113][114]. Moreover, ASX enhances apoptosis and decreases cell proliferation. ASX is able to enhance the cytotoxicity of the drugs with clinical activity in NSCLS, such as erlotinib, a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. The co-administration of erlotinib and ASX has increased cytotoxicity and inhibited cell growth in NSCLC cells, associated with the downregulation of xeroderma pigmentosum complementation group C (XPC) expression [114]. The overexpression of thymidylate synthase (TS) usually causes resistance to antitumor treatment, especially pemetrexed used in advanced NSCLC forms. ASX treatment decreases TS expression, both alone and in combination with pemetrexed. Moreover, ASX administration together with mitomycin C significantly reduces Rad51 expression, which exhibits high levels in chemoresistant carcinoma [115][116].

All these in vitro findings suggest that ASX may improve the efficacy of standard treatments in lung cancer. Some studies have also suggested that ASX could be used to treat gastric cancer, based on its role in necroptotic signaling [117].

Despite its biological activities, ASX has very low bioavailability, similar to other carotenoids [116][118]. When astaxanthin is administered orally, the bioavailability varies between 10 and 50% of the given dose [119]. The very poor bioavailability of ASX is due to dissolution limitations in gastrointestinal fluids and also to the saturated capacity of incorporation into bile micelles, which limits its absorption [120][121]. Being a very lipophilic compound, it has extremely low water solubility, which prevents its dispersibility and causes a low absorption rate [116][122]. After ingestion, ASX mixes with bile acid, forming micelles in the small intestine, partially absorbed by intestinal mucosa cells, which will incorporate astaxanthin into chylomicrons [103]. After their release into the lymph within the systemic circulation, chylomicrons with ASX are digested by lipoprotein lipase, ASX is assimilated with lipoproteins and transported to tissues, and chylomicrons remnants are quickly removed by the liver and other tissues [103]. In nature, astaxanthin is predominantly found in the form of mono- and diesters, being, respectively, esterified with one or two units of fatty acids in hydroxyl groups, or in the form of carotenoproteins when conjugated with proteins [119].

In order to improve the water solubility, stability, and bioavailability of ASX, several delivery systems have been developed, such as complex coacervation, liposomes, emulsions and nanoemulsions, microparticles, and polymeric nanoparticles [123][124][125]. Since lipid-based nanoparticles, such as liposomes, solid-lipid nanoparticles, and niosomes have limitations, such as poor water solubility and permeability, instability, rapid metabolism, and poor oral bioavailability, polymeric nanoparticles have begun to be used to overcome these limitations. Thus, after encapsulation in polymeric nanoparticles made from biodegradable natural polymers, such as polysaccharides and proteins, water solubility, stability, and absorption in the human body were enhanced [122][125]. In terms of nanoemulsion-based delivery systems, they provide improved physical stability and increase water dispersibility and bioavailability [114].

5. Quercetin

Quercetin is a flavonoid belonging to the flavonols group, present in a large variety of fruits—apples (*Malus domestica* (Suckow) Borkh.), grapes (*Vitis vinifera* L.), olives (*Olea europaea* Hoffmanns. and Link L.), citrus fruits such as oranges (*Citrus sinensis* (L.) Osbeck), and raspberries (*Rubus idaeus* L.)—vegetables—tomatoes (*Solanum lycopersicum* L.), onions (*Allium cepa* L.), broccoli (*Brassica oleracea* var. *italica* Plenck), and capers (*Capparis spinosa* L.)—drinks (tea and red wine), and herbal extracts [126]. In nature, quercetin is not present in the isolated form but is the aglyconic component of some glycosides, including rutin and quercitrin. In this form it abounds, in particular, in extracts of horse chestnut (*Aesculus hippocastanum* L.), *Gingko biloba* L., marigold (*Calendula officinalis* L.), hawthorn (*Crataegus monogyna* Jacq.), chamomile (Matricaria recutita L. and *Chamaemelum nobile* L.), lovage (*Levisticum officinale* W. D. J. Koch), and St. John's wort (*Hypericum perforatum* L.) [127][128].

Quercetin is capable of increasing the pro-apoptotic molecules BAX, caspase-3, caspase-9, and p53 and stimulating the mitochondrial apoptosis pathway, resulting in increased proapoptotic effects [129][130]. Another important feature of quercetin is related to the arrest of the cell cycle in the G1 phase by activating p21 and decreasing D1/Cd4 and E/Cdk2 ratios [131][132]. Several studies have demonstrated that quercetin can inhibit carcinogenesis and metastasis in cancer and is capable of stabilizing p53, a key molecule in cancer therapy involved in cell death and survival regulation [133].

In gastrointestinal cancer (GC), the genes encoding for the proteins urokinase plasminogen activator (uPA) and uPA receptor (uPAR) are strongly associated with this type of cancer, being a crucial pathway for tumor invasion. Quercetin has the ability to decrease the expression of these genes, strongly associated with the suppression of cell viability, migration, and invasion. Likewise, quercetin has antimetastatic effects in GC by interfering with uPA/uPAR systems, AMPKα, NF-kβ, ERK1/2, and PKC-δ regulation [134]. In patients with CRC carrying the KRAS mutant gene, quercetin decreases cell viability and increases apoptosis by AKT pathway repression and the activation of the c-Jun N-terminal kinase (JNK) pathway in mutant KRAS cells [135].

In prostate cancer, quercetin inhibits the expression of androgen receptor (AR) and AR-mediated PSA expression at the transcriptional level with the inhibition of tumor progression. Quercetin can suppress survival protein Akt and enhance prostate cancer apoptosis in a dose-dependent manner [136].

Quercetin decreases IGF1 levels and increases IGFBP3, which is associated with an increase in proapoptotic effects and a decrease in anti-apoptotic proteins BCL2 and BCL-XL [137].

Src is a non-receptor tyrosine kinase that is deregulated in many types of cancer. Quercetin has an anti-NSCLC effect in lung cancer by inhibiting the Src-mediated Fn14/NF-κB pathway [138].

The epigenetic mechanisms associated with quercetin are the suppression of Janus kinase 2 (JAK2) with the inhibition of the proliferation, invasion, and migration of cancer cells [139]. Quercetin can also enhance apoptosis

through its DNA-demethylating activity. Quercetin has an inhibiting effect on class I HDAC expression in leukemia cells due to increased proteasomal degradation [140]. Quercetin turns out to be a valid nutraceutical that can help reduce the formation of free radicals and pro-inflammatory substances, proving to be a valuable aid for human health.

Quercetin has also been shown to modulate the expression of microRNAs in different types of cancer by increasing the expression of tumor-suppressive miR-let-7, miR-15a, miR-16, miR-16, miR-22, miR-26, miR-200b-3p, miR-142-3p, miR-146a, miR-217, and miR-330 and decreasing the expression of oncogenic miR-27a, miR-155, miR-21, miR-19b, miR-148c [141].

The bioavailability of quercetin is generally poor and characterized by high interindividual variability, which could explain the conflicting results on quercetin bioactivities reported in various studies [142][143]. Pharmacokinetic studies indicate a low absorption of quercetin, with less than 1% of quercetin being absorbed in humans following oral administration [142][144]. The absorption of quercetin is related to its solubility in the vehicle used for administration [142][145]. Thus, the low solubility of quercetin in water, gastric fluids, and small intestine fluids will limit its absorption in the body [144][146]. The absorption of quercetin depends on its chemical structure. Thus, while quercetin aglycone is absorbed in both the stomach and small intestine, glycosylated forms of quercetin are not absorbed in the stomach and will be absorbed only in the small intestine, after deglycosylation, as quercetin aglycone. Quercetin biotransformation occurs by small intestinal and hepatic xenobiotic metabolism, which consists of three phases: phase I modification, phase II conjugation, and phase III elimination. Quercetin is rapidly eliminated via feces and urine. In addition to poor absorption, another factor limiting the bioavailability of quercetin is its hepatic biliary excretion, a significant proportion of absorbed quercetin being directed to biliary elimination and not to circulation [142][143].

Other factors that may affect quercetin bioavailability include the food matrix, nondigestible fiber, dietary fat, the presence of sugar moieties, and the botanical origin of quercetin. The results of a randomized crossover study, in which six women ingested the same amount of quercetin either in cereal bars or hard capsules, showed that the bioavailability of quercetin is higher when the quercetin aglycone is consumed as a whole food component [146][147]. In a study of rats, the influence of nondigestible oligosaccharides on the bioavailability of quercetin was examined. The co-administration of quercetin with short-chain fructooligosaccharides has been shown to improve the bioavailability of quercetin, as microbial degradation of the quercetin aglycone in the large intestine has been inhibited, thereby promoting the absorption of the quercetin glycoside [142][146]. Since quercetin aglycone is lipophilic, its co-ingestion along with fat has been able to increase the absorption of quercetin by incorporating it into micelles. This was observed in a study using pigs, but the improvement in the quercetin bioavailability in the case of fatty food ingestion was also demonstrated in another in vivo study in humans [142][146][147]. The bioavailability of quercetin may also be influenced by the presence or absence of the glucoside moiety, with studies in pigs showing the increased bioavailability of quercetin glycoside compared to quercetin aglycone, most likely due to the preferential absorption of quercetin glucoside, which is more water-soluble than quercetin aglycone [142]. In addition, the bioavailability of quercetin glycosides may be influenced by the type of sugar moiety [147]. Another factor on which quercetin bioavailability depends is its botanical origin. Thus, comparing the bioavailability of

different forms of quercetin derivatives from onions, apples, and tea, it was observed that quercetin glycosides from onions had the highest bioavailability. The bioavailability of quercetin in humans may also be affected by health status, gut microbiota, genetic factors, and oxidative stress [146]. Various approaches have been used to improve the water solubility and bioavailability of quercetin, such as encapsulation in nanoparticles, emulsions and nanoemulsions, hydrogels, cyclodextrin complexation, size reduction (nanosuspension, nanocrystals, nanorods), co-crystallization, and amorphous solid dispersions [144][146][148].

6. Epigallocatechin-3-Gallate

EGCG is the most abundant catechin in tea, especially in green tea (*Camellia sinensis* L.). EGCG is a polyphenol with antioxidant and anti-inflammatory action. Besides tea, it is also found in smaller quantities in other foods, such as carob (*Ceratonia siliqua* L.) flour, apples (*Malus domestica* (Suckow) Borkh.), blackberries (*Rubus plicatus* L. Weihe and Nees), raspberries (*Rubus idaeus* L.), pistachios (*Pistacia vera* L.), prunes (*Prunus domestica* L.), peaches (*Prunus persica* (L.) Batsch), and avocados (*Persea americana* Mill.). From the tea plant, for production, the leaf bud and the two adjacent leaves are used together with their stem. Green tea is very rich in polyphenols, and among them, EGCG is the most-studied active ingredient with the highest antioxidant activity [149].

EGCG, and tea polyphenols in general, are capable of mediating the epigenetic induction of metalloproteinase inhibitors (TIMP), such as TIMP-3, whose levels have a key role in suppressing the gelatinolytic activity of MMP-2 and MMP-9, involved in the metastatic process. Therefore, EGCG is considered a modulator of metalloproteinase activity, with benefits at oncological levels [150].

EGCG also has the ability to inhibit acute promyelocytic leukemia (APL) by inhibiting cell proliferation and promoting apoptosis [151]. In cell culture and animal models of prostate, breast, skin, liver, bladder, lung, and digestive tract cancer, EGCG induces the inhibition of cell proliferation and apoptosis by affecting the MAPK/ERK pathways and growth factors IGF1, IGF, and IGFBP-3. By inhibiting PI3K/AKT/p-BAD, a cell survival pathway, EGCG controls apoptosis. Moreover, EGCG is able to inhibit angiogenesis, invasion, and VEGF [152]. EGCG is an important regulator of cancer-associated microRNAs and upregulates miR-16, miR-210, and miR-330 and decreases miR-21 and miR-98-5p expression in liver, prostate, and lung cancer [153].

As concerns the intestinal absorption of EGCG, this process seems to show low efficiency, as EGCG lacks specific receptors for its absorption and is carried by passive diffusion (e.g., paracellular diffusion, transcellular diffusion) across epithelial cells. Following absorption, EGCG undergoes a phenomenon of active outflow, mediated by components of the efflux transport system (e.g., P-glycoprotein, multidrug resistance-associated proteins, breast cancer resistance proteins) that actively efflux intracellular EGCG to the extracellular intestinal space [154][155]. At the level of the small intestine and liver, EGCG is metabolized by phase II enzymes, releasing glucuronidated, sulfated, and methylated conjugates. EGCG metabolites are excreted through both bile and urine. EGCG can be further reabsorbed from the intestine through the enterohepatic recirculation process [156][157][158].

To capitalize on the therapeutic potential of EGCG in humans, despite its reduced bioavailability, high intakes have been suggested (e.g., the consumption of 8 to 16 cups/day of green tea) [159]. Nevertheless, using high doses of catechins may be of concern in the context of their dose-dependent toxic effects. A recent report by the European Food Safety Agency indicated a risk of liver damage following the intake of EGCG in the form of dietary supplements, at doses of 800 mg/day or above [160][161]. In order to manage these issues and improve the bioavailability of EGCG, several approaches have been identified. One approach involves the co-administration of EGCG with other bioactives. For instance, a formulation with ascorbic acid and sucrose has been demonstrated to enhance EGCG bioavailability by increasing its bioaccessibility and intestinal uptake from green tea [162]. Likewise, it has been suggested that the ingestion of EGCG on an empty stomach may improve its systemic absorption [163]. Moreover, the structural modification of EGCG by methylation, acyclization, or glycoside modification seems to allow the management of its premature degradation and reduced absorption rate [156][164]. Finally, one promising approach to protect EGCG against unfavorable gastrointestinal conditions and improve its bioavailability includes the design of nanocarriers. Examples of carriers developed for the nanodelivery of green tea catechins comprise surfactant-based nanovesicles (liposomes, phytosomes, niosomes, bilosomes), polysaccharide nanostructures, protein nanoparticles, nanoemulsions, and nanostructured lipid carriers [154][165].

7. Lycopene

Lycopene is a non-provitamin A carotenoid, present particularly in tomatoes (*Solanum lycopersicum* L.), but also in apricots (*Prunus armeniaca* S. X. Sun L.), guava (*Psidium guajava* L.), papaya (*Carica papaya* L.), watermelon (*Citrullus lanatus* subsp. *vulgaris* (Schrad.) Fursa), and pink grapefruit (*Citrus × paradisi* Macfad.). The level of ripeness in these fruits influences their lycopene content. For example, the content of lycopene is 50 mg/kg in ripe tomatoes, but only 5 mg/kg in unripe yellow tomatoes [166]. In addition to having a powerful antioxidant action, lycopene can improve the fluidity of the circulating blood mass and reduce the inflammatory response [167].

Carotenoids, as well as their metabolites and oxidation products, improve communication at the level of the intercellular junction gate GJC (Gap Junction Communication), which is considered one of the mechanisms of cancer prevention. GJC is deficient in many forms of cancer and the restoration of this function leads to cell proliferation reduction [168]. Several studies have demonstrated that lycopene is capable of modulating the expression of genes involved in inflammation, apoptosis, and cancer progression and, in this manner, reducing prostate cancer risk [169][170].

Although the majority of the lycopene in unprocessed food is found in the all-*trans* isoform, human serum and tissues have been reported to contain mainly the *cis* isomers of this carotenoid. A potential mechanism to explain this phenomenon could be an intestinal absorption that is preferential for the forms of *cis*-lycopene [171]. Indeed, evidence from early in vitro and animal studies has suggested that the *cis* isomers of lycopene have greater bioavailability than the all-*trans* form, possibly due to *cis* isomers showing a shorter length, higher solubility in mixed micelles, and/or a lower tendency to aggregate into crystalline structures [172]. However, more recent studies in human subjects have reported that there are no significant differences between *cis*-lycopene and all-

trans lycopene absorption, indicating heat-induced isomerization or enzymatic isomerization within body tissues as processes that could explain the enhanced *cis* isomeric profile in human serum and tissues [173].

As concerns the intestinal absorption of lycopene, this process occurs either by passive diffusion or via the scavenger receptor class B type 1 protein (SR-B1) transporter. Nevertheless, the intestinal absorption of lycopene seems to have limited efficiency [171]. In the study conducted by Moran et al. (2015), human subjects absorbed only about 24% of the ingested lycopene. Lycopene is mainly stored in the liver, but it can also accumulate within extrahepatic tissues (e.g., adipose tissue, adrenals, skin, kidneys, lungs, prostate, testes, ovaries, and breastmilk) [171][173]. During its initial metabolism, lycopene produces lycopenoids (e.g., APO-10′-lycopenoic acid). Some studies suggest that the health effects of lycopene are actually related to the biological activities of lycopenoids, but more research is required to clarify this aspect [174]. Lycopene is mainly excreted through the feces and in lower amounts through the urine [171].

In recent years, there has been a growing interest in identifying factors that could improve the bioavailability of lycopene from dietary sources such as tomatoes. The mechanical treatment of tomatoes (e.g., by mastication, grinding) appears to be important for lycopene bioaccessibility and hence for its plasmatic bioavailability [175]. Likewise, the heat processing of tomatoes may increase the bioavailability of lycopene in these foods by favoring its *trans*-to-*cis* isomerization. It has also been suggested by several studies that the addition of dietary fats (e.g., olive oil, avocado) to tomato dishes may increase the absorption and consequently the plasma levels of lycopene [176][177]. A recommendation has been issued to add a minimum of 10 g of fat in culinary preparations containing processed tomato products and 15 g of fat in fresh tomato recipes, respectively [171]. The encapsulation in nanoparticles of the lycopene extracted from food sources or biosynthesized also seems to help in solving its bioavailability issues and capitalizing on its nutraceutical potential [178].

Furthermore, there are several factors related to the characteristics of human subjects ingesting lycopene that have been reported to influence the bioavailability of this bioactive compound. Gender, adiposity, body mass index, and smoking habits appear to contribute to about 25% of the variation in serum lycopene concentrations [179]. In addition, there are studies to suggest that certain genetic variants linked to carotenoid metabolism may have an impact on lycopene bioavailability [179][180][181]. For example, the single nucleotide polymorphism rs6564851 in the β-carotene 15,15′-oxygenase-1 (BCO1) gene, which encodes for the BCO1 enzyme responsible for carotenoid cleavage in mammals, has been reported as being significantly associated with changes in lycopene circulating levels [179].

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