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REVIEW

Cancer Protective Role of Selected Dietary Polyphenols via Modulating Keap1/Nrf2/ARE and Interconnected Signaling Pathways

Md Arman Islam[a*], Maisha Maliha Medha[a*], Akhlak Un Nahar[a], Md Abdullah Al Fahad[a,b], Md Afjalus Siraj[c] and Veronique Seidel[d]

[a]Pharmacy Discipline, Life Science School, Khulna University, Khulna, Bangladesh; [b]Department of Regenerative Medicine, College of Medicine, Soonchunhyang University, Cheonan, Republic of Korea; [c]Department of Pharmaceutical Sciences, Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, Hilo, Hawaii, USA; [d]Natural Products Research Laboratory, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

ABSTRACT

The Kelch-like ECH associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response elements (ARE) signaling pathway is considered a master regulator of the cellular response against oxidative stress. Numerous studies have investigated the role of Keap1/Nrf2/ARE in the different stages of cancer development. A comprehensive literature search using the Google Scholar, PubMed and Science Direct databases was performed to retrieve information related to the cancer protective role of 21 selected dietary polyphenols via modulation of Keap1/Nrf2/ARE and interconnected signaling pathways/proteins (MAPK/ERK1/2, PI3K/Akt, PKD, JNKs, AMPK, NF-κB). Information on the anti-inflammatory and cytoprotective effects caused by the selected dietary polyphenols following Keap1/Nrf2/ARE modulation was also collected. The majority of the studies analyzed in this review demonstrated the cancer protective role of the selected polyphenols mostly *in-vitro*. Limited work was performed *in-vivo* and only one of the selected polyphenols was subjected to a clinical trial. It is hoped that this review will encourage further *in-vivo* studies to confirm the cancer protective role of methyleugenol, carnosol, and catechin, as well as further clinical trials to unambiguously establish whether the consumption of dietary polyphenols impacts on the incidence and progression of cancers in humans.

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ABBREVIATIONS: ROS: Reactive oxygen species; Keap1: Kelch-like ECH associated protein 1; Nrf2: Nuclear factor erythroid 2-related factor 2; ARE: Antioxidant response elements; GSH: Glutathione; MAPK: Mitogen activated-protein kinase; ERK1/2: Extracellular-regulated kinase 1/2; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; PKD: Protein kinase D; JNKs: c-Jun N-terminal kinases; NF-κB: Nuclear factor kappa B; PKC: Protein kinase C; AP-1: Activator protein-1; HIF 1α: hypoxia-inducible factor 1-alpha; MDA: Malondialdehyde; VEGF: Vascular endothelial growth factor; PAK-1: p21-activated kinase-1; NOX: NADPH oxidases; NFE2: Nuclear factor erythroid-derived 2; Neh: NRF2-ECH homology; sMAF: Small musculo-aponeurotic fibrosarcoma; BTB: Broad complex, tramtrack, bric-a-brac; IVR: Intervening region; Maf: Muscle aponeurosis fibromatosis; GST: Glutathione *S*-transferase; NQO1: NADPH quinine oxidoreductase; GCL: Glutamylcysteine ligase; GPx: Glutathione peroxidases; SOD: Superoxide dismutase; UGT: UDP-glucuronosyl transferase; HO-1: Heme oxygenase-1; Trx: thioredoxin; EH: Epoxide hydrolases; IL-1β: Interleukin-1β; PPARγ: peroxisome proliferator-activated receptor gamma; AMPK: AMP-activated protein kinase; ASK: Apoptosis signal-regulating kinase 1; BCL-2: B-cell lymphoma 2; HIPK2: Homeodomain-interacting protein kinase 2; PDGF: Platelet derived growth factor; EMT: Epithelial to mesenchymal transition; MMP-2: Matrix metalloproteinase-2; STAT3: Signal transducer and activator of transcription 3; LPS: Lipopolysaccharide; GSK3β: Glycogen synthase kinase-3 beta; NLRP3: NLR family pyrin domain containing 3; TNF-α: Tumor necrosis factor-α; mTOR: Mammalian target of rapamycin; TLR4: Toll-like receptor 4; NO: Nitric oxide; PGE2: Prostaglandin E_2; CAT: Catalase; OGG1: 8-oxoguanine glycosylase; TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin; SIRT1: Sirtuin 1; FOXO1: Forkhead box protein O 1; DENA: Diethylnitrosamine; TGF-β1: Tumor growth factor-β1; IKKβ: Inhibitor of nuclear factor kappa-B kinase subunit beta; GCLC: Glutamate cysteine ligase catalytic; GCLM: Glutamate cysteine ligase modifier; LTB4: Leukotriene B4; Syk: Spleen tyrosine kinase; PLA2: Phospholipase A_2; 5-LO: 5-lipoxygenase; AKR1B10: Aldo-keto reductase family 1 member B10; FTL: Ferritin Light Chain; GGTLA4: Gamma-glutamyltransferase-like activity 4; GCS: γ-glutamylcysteine synthetase; FKHR: Forkhead transcription factors; NSCLC: Non-small cell lung cancer cell; CCL5: Chemokine (C-C motif) ligand 5; iNOS: Inducible nitric oxide synthase;

CONTACT Afjalus Siraj afjalus.siraj@gmail.com; Veronique Seidel veronique.seidel@strath.ac.uk
*These authors contributed equally to this work.

COX-2: Cyclooxygenase-2; Wnt: Wingless-related integration site; 5-FU: 5-Fluorouracil; TPA: 12-*O*-tetradecanoylphorbol-13-acetate; EGF: Epidermal growth factor; PARP: Poly (ADP-ribose) polymerase; cGMP: Cyclic guanosine monophosphate; MT: Metallothionein; IGF II: Insulin-like growth factor II; JAK2: Janus kinase 2; TRAIL: TNF-related apoptosis-inducing ligand; PERK: Protein kinase RNA-like endoplasmic reticulum kinase; DNMT: DNA methyltransferase; HDAC: Histone deacetylases; NLCs: Nanostructured lipid carriers; MRP2: Multidrug resistance-associated protein 2; MCP-1: Monocyte chemotactic protein-1; VCAM-1: Vascular cell adhesion protein-1; MDR: Multi drug resistance; UGT1A: UDP glucuronosyltransferase 1 family, polypeptide A; HUVECs: Human umbilical vein endothelial cells; UGTs: UDP-glucuronosyltransferases; GCS: Glutamyl cysteine-synthetase; GR: Glutathione-reductase; TGM2: Transglutaminase-2; PTEN: Phosphatase and tensin homolog; CDK2: Cyclin dependent kinase 2: IRS-1: insulin receptor substrate 1

Introduction

Role of Keap1/Nrf2/ARE in Carcinogenesis

The overproduction of reactive oxygen species (ROS)—associated with mitochondrial cellular respiration, phagocytosis, digestion, aging tissues, and the metabolism of xenobiotics—generates high levels of free radicals in cells and causes oxidative stress. The latter has been strongly linked to carcinogenesis as it induces DNA mutations, promotes cancer cell growth and proliferation, stimulates angiogenesis and increases resistance to cell apoptosis and autophagy. Oxidative stress interferes with the mitogen activated-protein kinase (MAPK)/extracellular-regulated kinase 1/2 (ERK1/2), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), protein kinase D (PKD), c-Jun N-terminal kinases (JNKs), and nuclear factor kappa B (NF-κB), and other cell signaling proteins such as Ras, Raf, Bad, Bax, Bim and Foxo (1–4). At low doses, ROS promote tumor formation by influencing the expression of genes coding for proteins such as protein kinase C (PKC), Nrf2, MAPK, activator protein-1 (AP-1), NF-κB and the hypoxia-inducible factor 1-alpha (HIF-1α) involved in the growth of mutated cells. At high doses, they cause DNA point mutations, deletions, insertions, and chromosomal translocations, which promotes tumor cell mutagenesis by oncogene activation or tumor suppressor gene inactivation (e.g., p. 53) (5,6). Oxidative stress also induces mutation by causing lipid peroxidation and producing malondialdehyde (MDA) (7). In addition, ROS contribute to angiogenesis by regulating the vascular endothelial growth factor (VEGF), p21-activated kinase-1 (PAK-1) in Rac-associated cytoskeleton remodeling, and the ROS-generating enzymes (e.g., NADPH oxidases (NOX)) (8).

The Kelch-like ECH associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response elements (ARE) signaling pathway is considered a master regulator of the cellular response against oxidative stress (9,10). Nrf2, encoded upon activation of the nuclear factor erythroid-derived 2 (NFE2) gene, is a transcription factor with an N-terminal conserved region that has DNA-binding specificity. Nrf2 is highly expressed in the skin, lungs, gastrointestinal tract, and in metabolic and detoxifying organs such as the liver and kidneys (11,12). Nrf2 is a major mediator of a variety of functions contributing to cell survival, such as drug/xenobiotic metabolism, DNA repair, mitochondrial function, iron, lipid and carbohydrate metabolism, proteostasis and cell proliferation (13). Nrf2 contains 7 Nrf2-ECH homology (Neh) domains (Neh1-Neh7). The Neh1 domain recognizes ARE for the activation of gene transcription by heterodimerization with small musculoaponeurotic fibrosarcoma proteins (sMAF) K, G, and F. The Neh2 domain mediates Nrf2 ubiquitination and degradation by interacting with the Kelch domain of Keap1 (14). The latter is a cytoplasmic actin-bound adaptor protein that acts as an oxidative stress sensor and negative regulator of Nrf2 (15). Keap1 consists of the following domains: broad complex, tramtrack, bric-a-brac (BTB), Kelch. It also has an N-terminal region, an intervening region (IVR) and a C-terminal region (16). Under basal conditions, Nrf2 exists in the cytoplasm as an inactive complex bound to its negative regulator Keap. There, it undergoes rapid proteasomal degradation triggered by Cul3-directed polyubiquitination through the Keap1/Cul3 ubiquitin ligase (17). In the absence of oxidative stress (i.e., when the need for an antioxidative response is minimal), Nrf2 basal levels are low (18). Under oxidative stress, the highly reactive cysteine thiol groups in the IVR region of Keap1 are oxidized. This results in conformational variations in Keap1, causing its dissociation from Nrf2 (19–21). Once dissociated, the stabilized Nrf2 in the cytosol is translocated into the nucleus upon phosphorylation, along with de novo-synthesized Nrf2 proteins, forming heterodimers with nuclear small muscle aponeurosis fibromatosis

(Maf) proteins (22). These Nrf2/sMaf heterodimers then interact with a regulatory enhancer sequence named ARE which regulates about 250 human genes controlling the expression of antioxidant cytoprotective proteins (23). These restore cellular homeostasis following an oxidative insult by regulating inflammation, apoptosis, redox metabolism, iron and heme metabolism, phase-I, -II, and -III drug/xenobiotic metabolism and proteostasis (24,25). The phosphorylation reaction associated with Nrf2 activation is controlled by several kinases, including JNK, PI3K, PKC and ERK (26). Overall, the activation of the Keap1/Nrf2/ARE signaling pathway enhances cellular antioxidant capacity by upregulating the expression of genes coding for detoxifying and cytoprotective enzymes such as glutathione S-transferases (GSTs), NAD(P)H quinine oxidoreductase (NQO-1), glutamylcysteine ligase (GCL), glutathione peroxidases (GPx), superoxide dismutases (SODs), UDP-glucuronosyl transferases (UGTs), heme oxygenase-1 (HO-1), thioredoxin (Trx), and epoxide hydrolases (EH) (27–29). Nrf2 activation also promotes the synthesis/recycling of oxidized co-factors (e.g., glutathione) and detoxifying enzymes (30). As aforementioned, Keap1/Nrf2/ARE widely interacts with other signaling pathways and proteins to regulate the cell redox status. This includes MAPK/ERK1/2, PI3K/Akt, PKD, JNKs, AMPK, NF-κB and proteins such as Ras, Raf, Bad, Bax, Bim and Foxo (1–4). For example, it is known that inflammation induced by cytokines released via the NF-κB pathway is implicated in carcinogenesis through an increase in the production of ROS (31,32). Nrf2 activation inhibits oxidative stress by downregulating NAD(P)H oxidases and genes coding for interleukin-1β (IL-1β) and IL-6, and upregulating gene encoding for the peroxisome proliferator-activated receptor gamma (PPARγ) (33). Previously, we have reported the cancer chemopreventive role of dietary terpenoids via modulating the Keap1-Nrf2-ARE signaling pathway (34). Here, we describe and discuss the cancer protective role of selected dietary polyphenols via the same signaling system.

Role of Keap1/Nrf2/ARE in the Hallmarks of Cancer

Numerous *in-vitro* and *in-vivo* studies have investigated the role of Keap1/Nrf2/ARE in cancer, providing evidence for its dual effects (cancer-preventive and cancer-promoting) depending on the different stages of cancer development. Whilst the controlled/transient activation of Keap1/Nrf2/ARE in normal cells can prevent cancer initiation, its uncontrolled/prolonged activation in cancer cells drives cancer promotion, progression, and metastasis. The role of Keap1/Nrf2/ARE in sustained cell proliferation, apoptosis, angiogenesis, and metastasis is described below.

Sustained Cell Proliferation

Studies have demonstrated that Nrf2 targets the expression of genes controlling cell proliferation and survival. Experiments carried out using $Nrf2^{+/+}$ (wild-type) cells have revealed a significant increase in cell proliferation compared to $Nrf2^{-/-}$ cells. This has also been established In Vivo using $Nrf2^{-/-}$ mice (35,36).

Apoptosis

Apoptosis is generated in response to excessive ROS production, through oxidation of apoptosis signal-regulating kinase 1 (ASK) and activation of p38MAPK and JNK. In cancer cells, activation of the Keap1/Nrf2/ARE pathway leads to resistance to apoptosis via the enhanced expression of B-cell lymphoma-2 (BCL-2) and BCL-xL proteins. These suppress mitochondrial cytochrome C release and decrease caspase-3/7 activation (37). Nrf2 has also recently been found to target the homeodomain-interacting protein kinase 2 (HIPK2) gene which has anti-apoptotic functions (38,39).

Angiogenesis

It has been demonstrated that activation of Keap1/Nrf2/ARE promotes angiogenesis following increased Nrf2-induced NQO1 expression, which allows NQO1 to bind to HIF-1α, inhibiting HIF-1α degradation. Studies have revealed that blood vessel formation is markedly suppressed in Nrf2 knockdown tumor xenograft animal models. This anti-angiogenic effect is mediated via decreased levels of HIF-1α and of VEGF, platelet derived growth factor (PDGF), angiopoietin, and angiogenin (40).

Metastasis

In cancer cells, Keap1/Nrf2/ARE activation promotes the process of epithelial mesenchymal transition (EMT) important for metastasis, via downregulating the expression of the adhesion protein E-cadherin (41). It has also been reported that Nrf2 downregulation correlates with reduced expression of extracellular matrix remodeling enzymes such as the matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9) required for cancer cell migration (42). Other conflicting reports have indicated that

high NRF2 expression led to anti-metastatic effects (16,43,44). For a comprehensive review on the role of Keap1/Nrf2/ARE in other hallmarks of cancer (e.g., avoiding of immune destruction, tumor-promoting inflammation, genomic instability and others), the reader should refer to the work by de La Vega et al. (45). Two comprehensive updates provide additional details on the role of Keap1/Nrf2/ARE in metabolic reprogramming (46,47).

Methodology

A comprehensive literature search using the Google Scholar, PubMed and Science Direct databases was performed to retrieve information related to the cancer protective effects of 21 selected dietary polyphenols via modulation of Keap1/Nrf2/ARE and other interconnected signaling pathways/proteins (MAPK/ERK1/2, PI3K/Akt, PKD, JNKs, AMP-activated protein kinase AMPK, NF-κB). Information on the anti-inflammatory and cytoprotective effects caused by the selected dietary polyphenols following Keap1/Nrf2/ARE modulation was also collected. The polyphenols were selected based on their various roles in restricting different cancer types, their abundance in dietary foods, and the amount of published evidence for their cancer protective role compared to other compounds. The keywords used for this search included 'dietary polyphenols', 'antioxidant', 'free radical scavenger', and 'Nrf2', 'Keap1/Nrf2', 'Keap1/Nrf2/ARE', 'MAPK', 'PI3K', 'protein kinase B or Akt', 'ERK', 'AMPK', 'NF-κB' and 'cancer'. A further search using the keywords 'anti-inflammatory', 'hepatoprotective' and 'cytoprotective' was performed to collect information on additional Nrf2-modulated effects caused by the selected dietary polyphenols. Only research articles detailing *in-vitro* and *in-vivo* studies as well as clinical trials (419 in total) published in high-quality peer-reviewed journals between 2001–2022 were selected for the write-up of this review.

Cancer Protective Role of Plant-Based Dietary Foods via Modulation of Keap1/Nrf2/ARE and Interconnected Signaling Pathways

Multiple *in-vitro* and *in-vivo* studies have linked the effects of various cancer chemopreventive agents with activation of the Keap1/Nrf2/ARE pathway (48). Nrf2 activators exert cancer chemopreventive activity as they inhibit the metabolic activation of pro-carcinogens, block their reaching of target sites, prevent their interactions with cellular macromolecules (DNA, RNA, and proteins) as well as induce detoxification and increase the production of antioxidant enzymes (49). Various plant-derived natural products, including several from dietary sources, can modulate the Keap1/Nrf2/ARE pathway. This includes structurally-diverse phytoconstituents, such as isothiocyanates (50), garlic-derived organosulfur compounds (51), indoles from cabbage and broccoli (52), terpenoids from *Citrus* fruits and other dietary sources (53–55), and many aromatic and phenolic derivatives (56). Some of these natural products, such as sulphoraphane (in broccoli, Brussels sprouts, cabbage), curcumin (in turmeric), resveratrol (in grapes) or trigonelline (in coffee and fenugreek seeds), have been used as templates for the development of future cancer chemopreventive or anticancer drugs (13). The common dietary sources of the discussed polyphenols are presented in Table 1.

Selection of Polyphenols with Cancer Protective Activity via Modulation of the Keap1/Nrf2/ARE and Interconnected Signaling Pathways

The cancer protective role of 21 dietary polyphenols (Figure 1) in the modulation of Keap1/Nrf2/ARE and interconnected signaling pathways/proteins is described below and summarized in Table 2 and Figure 2.

Kaempferol

The prenylated chalcone xanthohumol **(1)** is the main flavonoid of the female inflorescences of hops (*Humulus lupulus* L.) and is found in beer (57). This compound exhibits a range of biological effects including cardioprotective, antioxidant, anti-inflammatory, antiviral, anti-obesity, as well as cancer chemopreventive and anticancer activity (221).

Xanthohumol activates the Keap1/Nrf2/ARE pathway by inducing the translocation of Nrf2 from the cytosol to the nucleus, as well as its binding to ARE (84). This activation upregulates the expression of several antioxidant enzymes, leading to decreased ROS generation and reduced GSH depletion (222,223). Xanthohumol has been shown to reduce cisplatin-induced inflammation and oxidation via activation of the Nrf2 pathway and upregulation of HO-1 expression (224), leading to a pro-apoptotic effect as apoptosis can be induced by inhibition of inflammation and oxidation (225). It has demonstrated cytoprotective and cancer chemopreventive activity on normal THLE-2 hepatocytes and hepatocellular carcinoma HepG2 cells via activating the Nrf2 pathway, upregulating phase-II enzymes, such as GSTs, HO-1,

Table 1. Common dietary sources of the 21 selected polyphenols.

Name	Common Dietary Sources (Scientific Name)	References
Xanthohumol (1)	Hops *(Humulus lupulus)*	(57)
Punicalagin (2)	Pomegranates *(Punica granatum)*	(58,59)
Resveratrol (3)	Grapes and wine (*Vitis vinifera)*; Peanuts (*Arachis hypogaea*); Soybean *(Glycine max)*	(60)
Methyleugenol (4)	Cloves *(Syzygium aromaticum);* Lemon grass *(Cymbopogon* spp.); Sweet basil *(Ocimum basilicum*); Nutmeg *(Myristica fragrans)*	(61–63)
6-Shogaol (5)	Ginger (Zingiber officinale)	(64)
Chlorogenic acid (6)	Robusta Coffee *(Coffea canephora, Coffea arabica);* Yerba Mate *(Ilex paraguariensis)*; Winter's Bark *(Drimys winteri)*	(65)
Ferulic acid (7)	Various fruits, grains and beverages as well as aubergines *(Solanum melongena*); Tomatoes *(Solanum lycopersicum*); Artichokes *(Cynara cardunculus var. scolymus);* Bamboo Shoots *(Bambusa vulgaris)*	(66)
Carnosic acid (8)	Rosemary *(Rosmarinus officinalis)*	(67)
Carnosol (9)	Rosemary *(Rosmarinus officinalis*); Mountain desert sage *(Salvia pachyphylla)*	(68)
Ellagic acid (10)	Cranberries *(Vaccinium macrocarpon);* Raspberries *(Rubus idaeus*); Walnuts (Juglans *regia*); Pecan nuts (Carya illinoinensis)	(69)
Apigenin (11)	Parsley *(Petroselinum crispum);* Celery (*Apium graveolens);* Chamomile tea (*Matricaria chamomilla)*	(70)
Catechin (12)	Green/White/Black tea *(Camellia sinensis)*	(71,72)
Epicatechin (13)	Green tea *(Camellia sinensis);* Grapes (*Vitis vinifera);* Cocoa *(Theobroma cacao)*	(73,74)
EGCG (14)	Green tea *(Camellia sinensis)*	(75)
Fisetin (15)	Strawberries *(Fragaria × ananassa);* Persimmon *(Diospyros kaki*); Grapes *(Vitis vinifera);* Apples *(Malus* spp.); Cucumber *(Cucumis sativus)*	(76)
Genistein (16)	Soybean seeds *(Glycine max)*	(77)
Isoorientin (17)	Bamboo *(Phyllostachys pubescens, Sasamorpha borealis);* Buckwheat (Fagopyrum esculentum) Foxtail lilies shoots (Eremurus spectabilis)	(78,79)
Quercetin (18)	Red wine, medicinal herbs, and Onion *(Allium cepa*); Blueberries *(Vaccinium sect. Cyanococcus*); Green tea *(Camellia sinensis)*	(80)
Luteolin (19)	Various medicinal herbs, and Celery *(Apium graveolen);* Green Peppers *(Capsicum annuum);* Parsley *(Petroselinum crispum);* Perilla leaves (*Perilla frutescens*); Chamomile tea *(Matricaria chamomilla)*	(81)
Rutin (20)	Asparagus *(Asparagus officinalis);* Buckwheat (Fagopyrum esculentum); Cherries *(Prunus avium);* Oranges *(Citrus × sinensis);* Grapes *(Vitis vinifera);* Grapefruits *(Citrus × paradisi);* Apricots *(Prunus armeniaca*); Apples (*Malus* spp.); Tea *(Camellia sinensis)*	(82)
Kaempferol (21)	Aloe *(Aloe vera);* Ivy gourd *(Coccinia grandis);* Drumstick tree *(Moringa oleifera*); Broccoli (Brassica oleracea); French beans (Phaseolus vulgaris); Tea (Camellia sinensis); Strawberries *(Fragaria × ananassa)*	(83)

and NQO1 combined with p53 induction (84). In PANC-1 and Mia-Pa-Ca-2 pancreatic cancer cells, the anti-inflammatory and pro-apoptotic effects of xanthohumol have been reported to reduce cell proliferation via Nrf2 activation and to increase the expression of antioxidant and detoxifying genes (SOD, NQO1, and GSTP) (85). Both *in-vivo* and *in-vitro* studies have showed that a combination of xanthohumol and phenethyl isothiocyanate induces apoptosis by modulating Nrf2 and abrogating NF-κB, signal transducer and activator of transcription 3 (STAT3), and the Akt/P70S6K signaling pathways in PSN-1 cancer cells. The same combination showed cytoprotective activity via activation of Nrf2 in non-cancerous MS1 cells (86). Xanthohumol ameliorates lipopolysaccharide (LPS)-induced lung injury, increasing the expression of antioxidative enzymes via Nrf2 activation associated with AMPK and glycogen synthase kinase-3 beta (GSK3β) phosphorylation. This suppressed the LPS-activated Txnip/NLR family pyrin domain containing 3 (NLRP3)

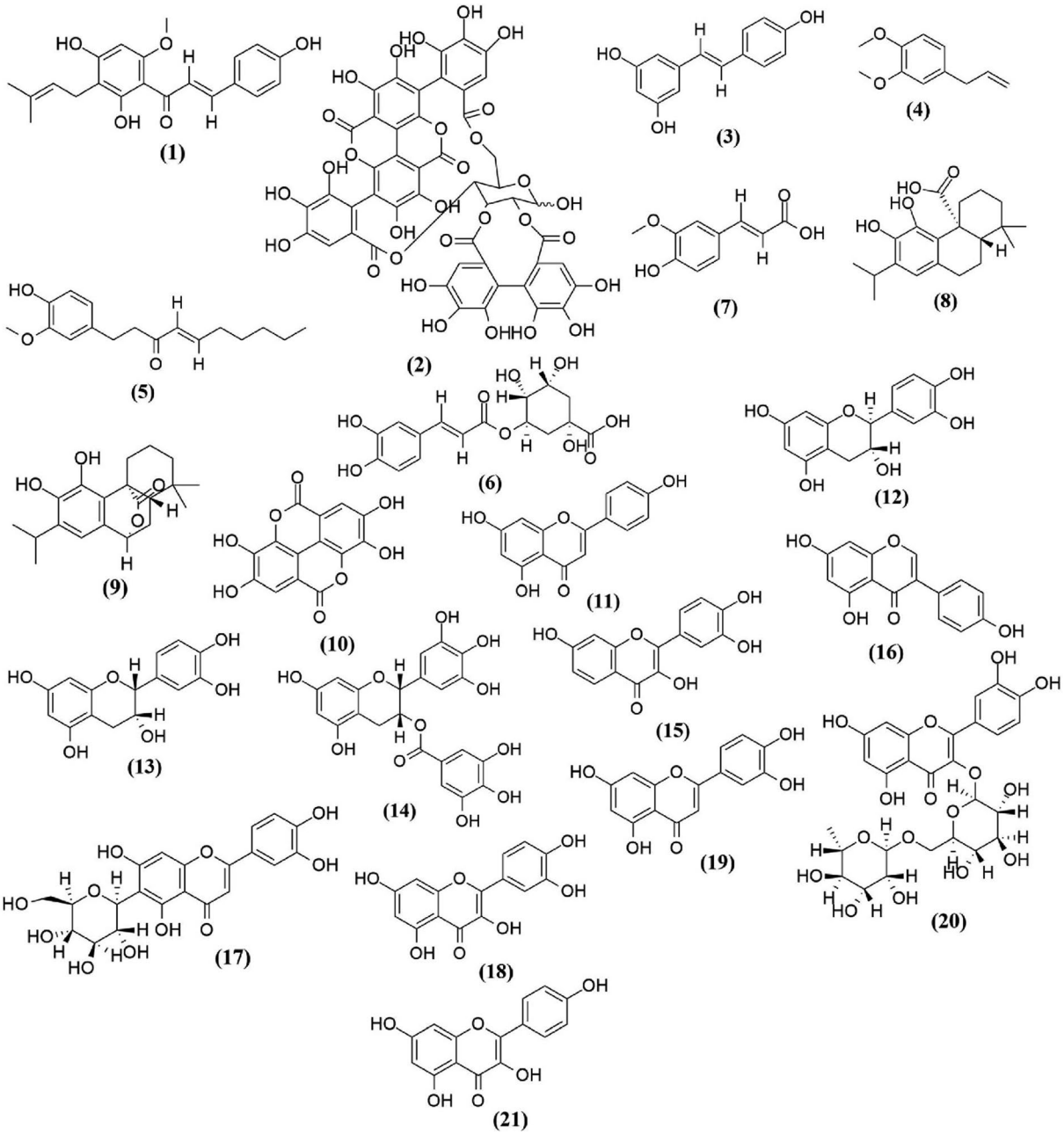

Figure 1. Chemical structures of the dietary polyphenols that modulate Keap1/Nrf2/ARE and interconnected signaling pathways. Here, **(1)** xanthohumol, **(2)** punicalagin, **(3)** resveratrol, **(4)** methyleugenol, **(5)** 6-shogaol, **(6)** chlorogenic acid, **(7)** ferulic acid, **(8)** carnosic acid, **(9)** carnosol, **(10)** ellagic acid, **(11)** apigenin, **(12)** catechin, **(13)** epicatechin, **(14)** EGCG, **(15)** fisetin, **(16)** genistein, **(17)** isoorientin, **(18)** quercetin, **(19)** luteolin, **(20)** rutin, and **(21)** kaempferol.

inflammasome and the NF-κB signaling pathway (222,226). In myeloid leukemia, the activation of PI3K/Akt, NF-κB, and other signaling pathways causes proliferation, transformation, and resistance to apoptosis (227). Xanthohumol is a potent inhibitor of T cell proliferation, cytokine production, and T cell-mediated cytotoxicity through the inhibition of NF-κB (228). It targets cell growth and angiogenesis, and causes impaired migration and invasion both *in-vivo* and *in-vitro* models of acute and chronic myeloid leukemia through inhibition of the PI3K/Akt and NF-κB signaling pathways (87). The inactivation of NF-κB can reduce the excessive production of inflammatory mediators, such as NO, IL-1β and tumor necrosis factor-α (TNF-α) in LPS-induced microglial BV-2 cells, thus exerting an anti-inflammatory effect (229). Xanthohumol also shows anticancer activity by downregulating topoisomerase-I and the expression of efflux drug transporters through induction of both caspase-dependent and caspase-independent apoptosis

Table 2. Cell signaling pathways and proteins targeted by the 21 selected dietary polyphenols with a cancer protective role.

Name	Signaling Pathways	Proteins	*In-vitro* activity on	*In-vivo* activity on	References
Xanthohumol **(1)**	p53, AMPK, STAT3, Akt, NF-κB	↑ HO-1, ↑ NQO1, ↑ GST, ↑ SOD, ↑ GSTP	Hepatocellular, pancreatic, chronic myeloid leukemia, colon, and prostate cancer	Pancreatic, leukemia	(84–90)
Punicalagin **(2)**	PI3/Akt, NF-κB, ERK	↑ HO-1	Cervical, osteosarcoma, and colon cancer	osteosarcoma	(91–94)
Resveratrol **(3)**	MAPK, PI3K/Akt, SIRT1, NF-κB, IKKβ, TGF-β1, Bax	↑ GST, ↑ HQO-1, ↑ HO-1, ↑ SOD-1, ↑ CAT, ↑ NQO1, ↑ OGG, ↑ GPx	Breast tumor, leukemia, renal, liver, and prostate cancer	Pancreatic, liver, colorectal, and breast cancer	(95–100)
Methyleugenol **(4)**	AMPK/GSK3b, ERK	↑ GCLC, ↑ GCLM, ↑ HO-1, ↑ NQO1	Cervical, retinoblastoma, leukemia, and colon cancer	N/A	(101–103)
6-Shogaol **(5)**	JNK, HO-1, COX2, iNOS, NF-κB, MAPK, PI3K/Akt	↑ AKR1B10, ↑ FTL, ↑ GGTLA4, ↑ HO-1, ↑ GCLC, ↑ GCLM, ↑ GCS, ↑ NQO1	Breast, lung, prostate, pancreatic, and endometrial cancer	Prostate, pancreatic, lung, and endometrial cancer	(104–110)
Chlorogenic acid **(6)**	NF-κB, IκBα, PI3K/Akt/mTOR, ERK1/2, p38 MAPK, JNK, HIF-1α/Akt, MMP-2 and -9, VEGF, EGF, IL-10, TGF-β, CD34	↑ GST, ↑ gGCL, ↑ NQO1, ↑ HO-1	Colon, breast, renal, lung, and hepatocellular carcinoma	Breast, lung, and hepatocellular carcinoma	(111–121)
Ferulic acid **(7)**	ERK1/2, NF-κB, IGF II, VEGF, PI3K-Akt	↑ HO-1, ↑ Bcl-2, ↑ NQO1, ↑ GSTA2, ↑ HO-1, ↑ PPARγ, ↓cyclin D1	Cervical, colorectal, prostate, melanoma, and breast cancer	Colorectal, melanoma, and breast cancer	(122–127)
Carnosic acid **(8)**	PI3K/Akt/mTOR, NF-κB, JNK, COX-2, JAK2-STAT3/Src-STAT3, TRAIL	↑ GSH, ↑ SOD, ↑ AKR1C2, ↑ HO-1, ↑ GDF15, ↑ PHLDA1, ↑ DDIT3, ↓Bcl-2, ↑ GCLC	Colorectal, breast, hepatocellular, gastric, and cervical cancer	Breast, hepatocellular, cervical, and liver cancer	(128–135)
Carnosol **(9)**	ERK, p38, JNK, PI3K, Sestrin2, MRP2, Akt, STAT3	↑ GSH, ↑ GCLC/GCLM, ↑ HO-1, ↑ NQO1	Colon, prostate, breast, and hepatocellular carcinoma	N/A	(136–139)
Ellagic acid **(10)**	ERK, JNK, PI3K/AKT/mTOR, STAT3, COX-2, NF-κB, AMPK, HIF-1α	↑ HO-1, ↑ SOD1, ↑ SOD2, ↑ GSH, ↑ γ-GCLC, ↑ NQO1	Endometrial, breast, prostate, pancreatic, bladder, and lung cancer	Endometrial, breast, pancreatic, bladder, and lung cancer	(140–145)
Apigenin **(11)**	MAPK, p38, ERK1/2 and JNK, PI3K/AKT/mTOR	↑ HO-1, ↑ SOD, ↑ CAT, ↑ GPx, ↑ NQO-1, ↓DNMT, ↓HDAC, ↑ GCLC, ↑ GCLM	Hepatocellular, skin, lung, prostate, colon, leukemia, and cervical cancer	Prostate, colon, leukemia, and cervical cancer	(70), (146–152)
Catechin **(12)**	ERK1/2, NF-κB, VEGF	↑ GCLC/GCLM, ↑ HO-1, ↑ NQO1, ↑ GPx, ↑ GR	Cervical, colon, and larynx carcinoma	N/A	(153–154)
Epicatechin **(13)**	PI3K/Akt, ERK, JNK1/2/3, p-38 MAPK, NF-κB, IL-10, IL-4	↑ SOD-1, ↑ GSH, ↑ HO-1, ↑ NQO1	Breast, colorectal, gastric, prostate, and leukemia	Leukemia	(155–159)
EGCG **(14)**	Akt, ERK1/2, p38, MAPK, Nrf2-UGT1A, VEGF, COX-2, IL-6, HIF-1α	↑ HO-1, ↑ GST, ↑ NQO1	Colorectal, lung, endometrial, and breast cancer	Colorectal, breast, esophageal, gastric, lung, neural, oral, and prostate cancer	(160–164)
Fisetin **(15)**	ERK, JNK, p38/MAPK, PI3K/Akt/mTOR, COX-2, Wnt/EGFR/NF-κB, eNOS, VEGF, iNOS	↑ HO-1, ↑ GCLC, ↑ GCLM, ↑ NQO1, ↑ GPx, ↓MDA, ↓cyclin D1, ↓survivin	Cholangiocarcinoma, oral, breast, bladder, colorectal, prostate, pancreatic, and cervical cancer	Breast, colorectal, pancreatic, and cervical cancer	(165–173)
Genistein **(16)**	ERK1/2, PKC, PI3K/Akt, SIRT1, NF-κB	↑ HO-1, ↑ NQO-1, ↑ SOD, ↑ CAT, ↑ GSH, ↑ GCLC, ↓Bcl-2	Prostate, pancreatic, breast, leukemia, bladder, and lung cancer	Pancreatic, leukemia, bladder, and lung cancer	(174–179)
Isoorientin **(17)**	SIRT1/SIRT6, AMPK/Akt/GSK3β, PI3K/Akt, JAK/STAT3, Wnt/β-catenin	↑ GCLC, ↑ GCLM, ↑ HO-1, ↑ NQO1, ↑ Trx-1	Liver, pancreatic, skin, lung, and oral cancer	Oral cancer	(180–184)
Quercetin **(18)**	p38-MAPK, PI3K/Akt/mTOR, STAT1, NF-κB, JNK/ERK MAPK	↑ GSH, ↑ GCS, ↑ GPx, ↑ GR, ↑ GCLC, ↓MDA, ↑ SOD, ↑ HO-1, ↑ CAT, ↑ GST, ↓Bcl-2	Liver, colon, breast, prostate, and mesothelioma	Prostate, and lung cancer	(80), (185–191)
Luteolin **(19)**	ERK1/2, NF-κB/p53, PI3K/Akt, mTOR, SIRT1, ROS/JNK, K-ras/GSK-3β/NF-κB	↑ HO-1, ↑ GCLC, ↑ GCLM, ↑ GSH, ↑ NQO1, ↑ SOD, ↑ GPx, ↑ CAT, ↓MDA, ↑ TRX1	Colorectal, lung, breast, bladder, and esophageal cancer	Breast, bladder, pancreatic, and esophageal cancer	(81), (192–200)
Rutin **(20)**	PI3K/Akt, SIRT1, STAT3/NF-κB, JNK, AP-1, and p38 MAPK, Wnt/β-catenin, COX-2, iNOS, TNF-α,	↑ HO-1, ↑ NQO-1, ↑ GST, ↑ Mn-SOD, ↓Bcl-2	Colon, lung, gastric, prostate, breast, brain, and leukemia	Cervical, breast, and colorectal cancer	(201–210)
Kaempferol **(21)**	p38, ERK1/2, JNK, SIRT1, PARP1, AMPK, PKCδ/MAPK/AP-1, IRS-1, Akt/ PI3K, MEK1/2, ERK-NFκB-cMyc-p21-VEGF, NF-κB	↓HO-1, ↑ SOD, ↑CAT, ↑ GSH, ↓NQO1, ↓AKR1C1, ↓GST	Pancreatic, hepatocellular, breast, cervical, colon, ovarian, and gastric cancer	Gastric, lung, and breast cancer	(211–220)

↑ indicates upregulation; ↓ indicates downregulation.

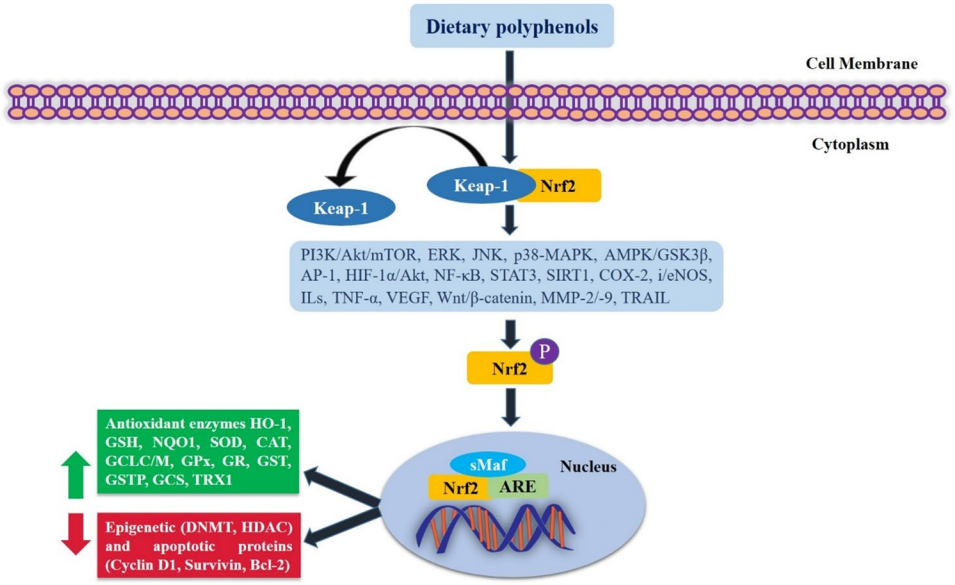

Figure 2. Cancer protective role of dietary polyphenols via modulating Keap1/Nrf2/ARE and interconnected signaling pathways.

(230,231). It has been reported to significantly alleviate the proliferation of HCT116-derived human colon cancer cells upon inducing apoptosis via activation of death-receptors as well as mitochondrial-mediated programmed cell death pathways by downregulation of Bcl-2 and activation of the caspase cascades (88). In human prostate cancer cells, it induces apoptosis by activating the pro-apoptotic proteins Bax and p53, decreasing the activation of anti-apoptotic NF-κB (89) and inhibiting Akt, NF-κB, p-mammalian target of rapamycin (mTOR) and NF-κB-regulated anti-apoptotic proteins Bcl-2 and survivin (90).

Punicalagin

The ellagitannin punicalagin **(2)** is the main bioactive constituent of pomegranate (*Punica granatum)* fruit, husk, and juice (58,59). This compound has antioxidant, anti-inflammatory (232), antiviral (233), anti-atherosclerotic (234), antimicrobial (235), anti-quorum sensing (236) and antiproliferative activity (237).

Punicalagin activates the Nrf2 pathway by decreasing Keap1 levels via activation of the PI3K/Akt pathway which causes the dissociation of Nrf2 from Keap1 and increases nuclear translocation of Nrf2, thereby inducing HO-1 expression. These events, along with the reversal of the LPS-induced reduction of SOD1 mRNA expression, give punicalagin its protective effect against LPS-induced oxidative stress (238). Punicalagin has been demonstrated to protect from heat stress-induced intestinal epithelial cell damage and cell death (239). It also acts as an anti-mutagenic agent by inhibiting DNA adducts caused by the induction of phase-II enzymes (240). The upregulated HO-1 is at the core of the Nrf2-mediated NF-κB inhibition; the pathway involved in the cytokine production (241). Whilst activation of the NF-κB pathway plays a pivotal role in tumor cell progression, growth, proliferation and resistance to apoptosis, inactivation of NF-κB plays a cancer protective role as it activates the Keap1/Nrf2/ARE pathway (225). The inhibition of the NF-κB pathway by punicalagin can impede cancer cell proliferation and enhance cell apoptosis in cervical cancer ME-180 cells and osteosarcoma (91,92). A tumor xenograft mouse model shows that punicalagin is able suppress the growth of osteosarcoma and inhibit angiogenesis via suppression of NF-κB activation (92). The TNFR-induced Akt activation, required for NF-κB activity, is also abrogated by punicalagin which is responsible for inhibiting cell proliferation and induction of apoptosis in human colon cancer cells (93,94). Studies have also shown that punicalagin exerts its anti-inflammatory activity via inhibition of the NF-κB and MAPK pathways mediated by toll-like receptor 4 (TLR4) mRNA expression. This anti-inflammatory effect is also mediated via the inhibition of the production of pro-inflammatory cytokines and other factors such as nitric oxide (NO), prostaglandin E_2 (PGE2), IL-1β, IL-6, and TNF-α (242). The Keap1-Nrf2 activation induced by punicalagin has been shown to reduce palmitate-induced lipotoxicity, including attenuation of mitochondrial

membrane potential loss, ATP depletion and ROS generation by the ERK/Nrf2 pathway and increase the viability of hepatocytes by blocking mitochondria-mediated caspase-dependent apoptosis (58).

Resveratrol

Resveratrol **(3)** is a stilbene that has been identified in more than 70 plant species, and predominantly occurs in grapes' skin and seeds, as well as in red wines (60). Resveratrol has antioxidant, anti-inflammatory, and anticancer activity (211).

It activates the Nrf2 signaling pathway by causing dissociation of Nrf2 from Keap1 and its translocation into the nucleus, leading to the activation of ARE-driven gene promoters (243). This activation of ARE downstream genes causes the scavenging of ROS that are responsible for DNA damage and the activation of phase-II enzymes (GST and HO-1) resulting in the detoxification of carcinogens (99,244). Resveratrol has been reported to protect porcine intestinal epithelial cells from oxidative stress through the PI3K/Akt-mediated Nrf2 signaling pathway by upregulating HO-1, SOD-1, and catalase (CAT) expression levels (245). It has been shown to prevent the formation of 17,β-estradiol-induced breast tumors by upregulating antioxidant genes NQO1, SOD3, and 8-oxoguanine glycosylase (OGG1) and thereby protects cells against oxidative DNA damage (95). The upregulation of NQO1 expression caused by resveratrol can protect leukemic cells from DNA adducts formation (246) and to decrease estrogen metabolism in 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced breast cancer MCF-10F cells (247). As an Nrf2 activator, resveratrol has been shown to decrease the growth and clonogenic potential of breast cancer MCF-7 cells exposed to doxorubicin, resulting in the inhibition of apoptosis, autophagy, and inflammation. In the ovaries, resveratrol can decrease the oxidative stress caused by chemotherapy by upregulating Nrf2 and activating the sirtuin 1 (SIRT1)/forkhead box protein O1 (FOXO1) pathway. In the presence of the cytotoxic agent sitagliptin, resveratrol was shown to ameliorate renal cell carcinoma showing antioxidant activity through restoring Nrf2/HO-1 content (96). Resveratrol also attenuates diethylnitrosamine (DENA)-induced liver tumorigenesis by modulating Nrf2 signaling pathway and suppressing oxidative stress and inflammatory cytokines (97). It inhibits ROS production by activating the Nrf2 pathway, reducing the expression of Keap1 and inhibiting NF-κB activation (248). The latter is caused by the inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ)-mediated IκBα phosphorylation by resveratrol (249). A number of reports have shown that NF-κB is an important inflammatory transcriptional regulator that can be activated by ROS (250). Thus, resveratrol acts as an anti-inflammatory agent by blocking IL-1β, TNF-α and NF-κB activation. These inflammatory factors play a role in the development of carcinogenesis including tumor growth, angiogenesis, invasion, and metastasis (251). Resveratrol has shown apoptotic and antiproliferative activity on human prostate cancer cells mediated by NF-κB inhibition (98). Resveratrol also causes the accumulation of Nrf2 in the cytoplasm and inhibits Nrf2-dependent transcription via SIRT1 deacetylase activity, in both K562 leukemia and HepG2 hepatocellular carcinoma cells, demonstrating its effect in both Nrf2 accumulation and translocation (99). *In-vivo* studies carried out on resveratrol showed that it suppresses pancreatic cancer (by abrogating PI3K and Akt phosphorylation), liver cancer (by enhancing Nrf2 expression), colorectal cancer (by increasing Bax expression), and breast cancer (by suppressing tumor growth factor-β1 (TGF-β1) and NF-κB expression) (100). A number of clinical trials have been conducted to evaluate the effectiveness of resveratrol on patients with prostate, colorectal and breast cancer. It was concluded that resveratrol was an unlikely candidate for prostate cancer, but showed a very slight effect on colon cancer and a promising effect on breast cancer, respectively (252).

Methyleugenol

Methyleugenol **(4)** is a phenylpropene found in the essential oils of clove, sweet basil, lemon grass, nutmeg and pimento (61). This compound is commonly used as a flavoring additive (253). It has anti-allergic, antinociceptive, antioxidant, anti-inflammatory (62,63), and anticancer (254) activity. It can also ameliorate cerebral ischemic injury (255).

Studies have revealed that methyleugenol can enhance the nuclear translocation of Nrf2, reduce Keap1 levels, and increase ARE activity (256). This compound has demonstrated antioxidant activity on different cell lines by scavenging ROS, decreasing superoxide generation along with increasing SOD, CAT and GSH (254). Its beneficial effects in ischemic cell injury both *in-vivo* and *in-vitro* have been attributed to its ability to scavenge ROS and generate an antioxidant effect via Nrf2/ARE activation (254). It also upregulates the expression of antioxidant enzymes, such as glutamate cysteine ligase catalytic (GCLC), glutamate cysteine ligase modifier (GCLM),

HO-1, and NQO1 by activating the Nrf2/ARE signaling pathway via activation of the AMPK/GSK-3β and ERK pathways (257). Methyleugenol was found to have anticancer activity in cervical cancer individually or in combination with cisplatin by inhibiting cell growth, inducing cell apoptosis, mitochondrial membrane potential loss and caspase 3 activity (101).It has also been reported to reduce cell viability, impede the expression of the PI3K/mTOR/Akt pathway and induce G_2/M cell cycle arrest in human retinoblastoma cancer cells (102). It has anticancer activity against leukemia cells (HL-60) and human colon carcinoma cells (103). Methyleugenol also exerts an anti-inflammatory effect by suppressing the release of pro-inflammatory cytokines, such as TNF-α, IL-4, PGE2, PGD2, leukotriene B4 (LTB4), and LTC4 via suppressing the activation of spleen tyrosine kinase (Syk), ERK1/2, p38, JNK, c phospholipase A_2 (PLA2), and 5-lipoxygenase (5-LO) (62). To the best of our knowledge, no *in-vivo* studies have been carried out to investigate the cancer protective role of methyleugenol via modulation of Keap1/Nrf2/ARE and interconnected pathways.

6-Shogaol

The polyphenol 6-shogaol **(5)** is the main bioactive constituent of dried or cooked ginger (*Zingiber officinale*). This compound displays a range of biological properties, including anti-inflammatory, analgesic, antipyretic, cancer chemopreventive and antioxidant activity (64).

It has been shown to decrease Keap1 levels by upregulating, phosphorylating, and translocating Nrf2 *in-vitro* and *in-vivo*, resulting in the upregulation of Nrf2 target genes including aldo-keto reductase family one member B10 (AKR1B10), Ferritin Light Chain (FTL), gamma-glutamyltransferase-like activity 4 (GGTLA4), HO-1, GCLC and GCLM. This activation of Nrf2 signaling enhances cellular antioxidant activity, GSH levels and ARE promoter activity (258). 6-shogaol activates Nrf2 via the JNK-mediated pathway, causing an increase in JNK activation and in the expression of γ-glutamylcysteine synthetase (GCS) and HO-1 (259,260). 6-shogaol also activates Nrf2 in PC12 cells and provides cytoprotection against oxidative stress (261). An analog of 6-shogaol, named 3-phenyl-3-shogaol (3-Ph-3-SG), has also been reported to provide cytoprotection by inducing the ARE-driven genes NQO1 and HO-1 and abrogate cancer cell invasion by suppressing NF-κB signaling (262). The latter causes inhibition of PMA-stimulated MDA-MB-231 breast cancer cell invasion via downregulating MMP-9 expression (104). Besides this, the blocking of Akt and downstream targets (including the mTOR, forkhead transcription factors (FKHR) and GSK-3β) by 6-shogaol has been reported to inhibit the survival of non-small cell lung cancer (NSCLC) cells (105). Here, 6-shogaol induces apoptosis by causing cell cycle arrest in G_1 or G_2/M phase. Its suppression of the Akt kinase activity results in reduced STAT3 activity and decreased expression of cyclin D1/3, and Akt signaling (263). The inhibition of STAT3 activity and NF-κB signaling by 6-shogaol has an effect on prostate cancer cells too, both *in-vivo* and *in-vitro*. 6-Shogaol causes a decrease in NF-κB target genes and protein levels, including cyclin D1, survivin, and cMyc, and modulates the mRNA levels of chemokines, cytokines, cell cycle, and apoptosis regulatory genes, such as IL-7, chemokine (C-C motif) ligand 5 (CCL5), Bax, Bcl2, p21, and p27 (106). In human pancreatic tumors, 6-shogaol blocks the growth of tumor cells and acts as adjuvant to potentiate gemcitabine via suppression of TLR4/NF-κB-mediated inflammatory pathways linked to tumorigenesis (107). 6-shogaol has an effect on pathways which is regulated for the prevention of carcinogenesis. Thus, the over expression of MAPKs (ERK1, JNK1 & p38) on UVB-induced HaCaT cells is minimized by 6-shogaol, thereby protects against UVB-induced oxidative skin damage (264). This compound also causes attenuation of several pro-inflammatory mediators in response to UVB, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), MMP, cell adhesion molecules, chemokines and cytokines (258). As an anti-inflammatory agent, 6-shogaol has been shown to increase HO-1 levels by attenuating COX-2, iNOS, NF-κB and MAPK signaling. It also helps in reducing edema by inhibiting leukocyte infiltration into inflamed tissue (265). Interestingly, one study has indicated that a novel potent Nrf2 activator molecule called (1E,4E)-1-(4-hydroxy-3-methoxyphenyl)-7-methylocta-1,4,6-trien-3-one (SA), synthesized from 6-shogaol acted as a Michael acceptor to cause dissociation of Nrf2 from Keap1, inhibit Nrf2 ubiquitination and activate the Nrf2 response (266). Finally, 6-shogaol exerts activity against human endometrial cancer via mediating ROS generation both *in-vitro* and *in-vivo* (108). It is also able to inhibit metastasis in endometrial carcinoma by triggering PI3K/Akt signaling both *in-vitro* and *in-vivo* (109). Other *in-vivo* studies have established the activity of 6-shogaol in prostate and lung cancer (106,110).

Chlorogenic Acid

The polyphenol chlorogenic acid **(6)**, also known as 3-caffeoylquinic acid (3-CQA), is mainly found in coffee (*Coffea canephora, Coffea arabica)* and mate

(*Ilex paraguariensis*) plants as well as in some fruits and vegetables (65). It exerts antioxidant, anti-inflammatory (267) and anti-carcinogenic activity (119).

Several chlorogenic acid derivatives are found in plants. These include 3-caffeoylquinic acid (3-CQA), 4-caffeoylquinic acid (4-CQA), 5-caffeoylquinic acid (5-CQA), 3,4-dicaffeoylquinic acid (3,4-diCQA), 3,5-dicaffeoylquinic acid (3,5-diCQA), and 4,5-dicaffeoylquinic acid (4,5-diCQA) which interact with Keap1-Nrf2 complex to activate Nrf2 signaling (268). This activation leads to an increased nuclear translocation of Nrf2 followed by enhanced expression of ARE-dependent genes coding for the phase-II enzymes GST, γ – GCL, NQO1, and HO-1 in colon carcinoma HT29 cells (111). Pretreatment with chlorogenic acid has been shown to protect from CCl_4-induced liver injury via activation of the Nrf2 pathway and suppression of NLRP3 inflammation (269). The activation of Nrf2/ARE also interacts with the phosphorylation of IκB and suppresses the activation of NF-κB (270). In LPS-induced inflammation, chlorogenic acid alleviates the symptoms and inhibits the LPS-induced oxidative stress through modulation of the NF-κB/MAPK pathway and nuclear translocation of Nrf2, respectively (271). In breast cancer, chlorogenic acid enhances antitumor immunity, exerts antitumor and anti-metastatic effects by impairing the NF-κB/EMT (120) and β-catenin of wingless-related integration site (Wnt) signaling pathways (272). Chlorogenic acid is also reported to kill MDA-MB-231 and MCF-7 cells by binding and stimulating the translocation of PKC, an important molecule for malignant tumor (112). Chlorogenic acid protects against cellular oxidative damage and renal cell carcinoma by activating Nrf2/ARE and modulating the PI3K/Akt pathway (113). It has been shown to exert an inhibitory effect on the PI3K/Akt/mTOR pathway in A498 kidney cancer cells (114). Chlorogenic acid also induces p38 MAPK and JNK gene expression, affecting apoptosis-related genes that are involved in oxidative stress in lung cancer cells (115). It also has the ability to induce ROS generation and exert cytoprotective effects on human colon cancer cells (116). The generation of ROS promotes anti-tumorigenic signaling and triggers oxidative stress–induced cancer cell death showing the dual characteristics of ROS (273). Chlorogenic acid also acts as a chemosensitizer of 5-fluorouracil (5-FU) chemotherapy, displaying a synergistic effect in combination with 5-FU, and inactivates ERK through the overproduction of ROS in HepG2 and Hep3B hepatocellular carcinoma cells (117). It has *in-vitro* activity against the proliferation of A549 human cancer cells and the 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced neoplastic transformation of JB6 P + cells (274). Both *in-vitro* and *in-vivo* studies have reported that chlorogenic acid is active against lung cancer via disruption of the binding of annexin A2 to the p50 subunit of NF-κB (118). Chlorogenic acid also has *in-vitro* and *in-vivo* anti-angiogenic activity via inhibition of HIF-1α/Akt signaling (275). It has been demonstrated to suppress the proliferation of HepG2 hepatocellular carcinoma cells by inactivating ERK1/2, MMP-2 and -9 expression in a xenograft model (119). Studies have also reported the effect of chlorogenic acid *in-vitro* and *in-vivo* against breast cancer via inhibition of NF-κB, VEGF, EGF, IL-10, TGF-β, and CD34 (120,121).

Ferulic Acid

Ferulic acid **(7)** a caffeic acid derivative found abundantly in vegetables (aubergines, tomatoes, artichokes), fruits, grains, and some beverages. This compound displays a range of biological effects in diseases that are linked with cancer, Alzheimer's disease, diabetes mellitus, skin and cardiovascular disorders (66).

Ferulic acid modulates the Keap1-Nrf2 pathway, causing dissociation of the Keap1/Nrf2 complex, increases Nrf2 transcription (276) and therein enhances expression of Nrf2-mediated phase-II enzymes, including NQO1, GSTA2 and SOD (277). It has been found to reduce serum TNF-α and IL-1β, hepatic NF-κB, p65, Bax, and caspase-3, and increase Bcl-2, Nrf2, NQO1, HO-1, and PPARγ, thereby attenuate oxidative stress, inflammation, and cell death (278). It causes activation of Nrf2 and enhances ARE promoter activity via phosphorylating ERK1/2 in PC-12 cells (279). The activation is caused by induction of Nrf2 nuclear translocation and transcriptional activity which significantly upregulates the HO-1 mRNA and protein expression controlled by the ERK signaling pathway (280). The activation of Nrf2/HO-1 increases antioxidant defenses via activating ARE-mediated genes leading to ROS scavenging and protection against γ-radiation-induced oxidative stress (281). NF-κB signaling is responsible for the development and progression of several human cancers (282). Blocking this pathway and activating antioxidative enzymes via Nrf2/ARE signaling abrogates the initiation of carcinogenesis. Ferulic acid can inhibit IL-6 and NF-κB promoter activity upon reduction of the nuclear translocation of Nrf2 and NF-κB through reduced expression of phosphorylated IKK (283). In cervical cancer cells, ferulic acid induces MMP-9

mRNA expression and G_0/G_1 phase blocking by increasing p53 and p21 along with decreasing autophagy related proteins (122). On the other hand, in HCT 15 colorectal cancer cells, it downregulates the human epidermal growth factor (EGF) receptor that is a vital for inducing colorectal cancer (123). It protects PC-3 prostate cancer cells by inducing apoptosis and cell cycle arrest (124). It exhibits antitumor activity against breast tumor cells both *in-vitro* and *in-vivo* through suppression of EMT (125). Ferulic acid, when administered together with poly (ADP-ribose) polymerase (PARP) inhibitors, increases breast tumor cells sensitivity to PARP inhibitors (284), exerting their protective effects through the regulation of various signaling pathways, including MAPKs, HIF-1α, Nrf2 and NF-κB (285). It has also been reported to reduce the LPS-induced overexpression of pro-inflammatory enzymes, such as iNOS and the subsequent excessive production of NO and cyclic guanosine monophosphate (cGMP) in intestinal Caco-2 cell monolayers. Two ferulic acid derivatives, iso-ferulic acid and dihydroferulic acid, and their glucuronidated and sulfated metabolites can decrease the nuclear translocation of NF-κB by promoting Nrf2 expression and controlling the activation of MAPK, p38, ERK and Akt (286). In LPS-activated RAW 264.7 mouse macrophages, ferulic acid inhibits the expression of inflammatory mediators, such as IL-6, TNF-α and iNOS and activates the expression of antioxidant metallothioneins (MT-1, MT-2) (283). A recent study used *in-vivo* and *in-vitro* models to assess the effect of ferulic acid lipid nanocapsules in colorectal cancer. These showed potential activity via suppressing the expression of cyclin D1, insulin-like growth factor II (IGF II), and VEGF, as well as via auto-regulating the apoptotic/anti-apoptotic gene BAX/Bcl-2 (126). Ferulic acid also exhibits anti-angiogenic and antitumor potential against melanoma, both *in-vivo* and *in-vitro*, via blocking PI3K-Akt signaling (127).

Carnosic Acid

Carnosic acid **(8)** is a major polyphenol in rosemary (*Rosmarinus officinalis*) with various biological properties, such as antioxidant, anti-inflammatory, neuroprotective and anticarcinogenic activity (67). Carnosic acid contains a catechol group that converts into electrophilic quinones upon oxidation, and this electrophilic nature helps in interacting with the cysteine residues of Keap1, activating the Keap1/Nrf2/ARE pathway and the synthesis of antioxidant enzymes (287).

Along with its effect on the Keap1/Nrf2/ARE pathway, the cytoprotective effect of carnosic acid also involves inhibition of the PI3K/Akt and NF-κB pathways (288,289). NF-κB activation is a key factor involved in the release of pro-inflammatory cytokines and inflammation-associated cancer (290). Both PI3K/Akt/mTOR and NF-κB pathways are important in chemoresistance and survival of cancer cells and are considered potential targets for cancer treatment (291,292). Carnosic acid has been reported to attenuate pro-inflammatory cytokine mRNA and protein levels in the colon of mice, as well as upregulate GSH and SOD activity and downregulate iNOS and MDA levels (293). Carnosic acid has been found to downregulate the expression of COX-2 at both the mRNA and protein levels in Caco-2 human colorectal cancer cells (128). This COX-2 inhibition is interrelated with NF-κB inactivation (294). One study revealed that carnosic acid, encapsulated into albumin nanoparticles, is able to mediate apoptosis to in MCF-7 breast and Caco-2 colorectal cancer cells (129). This effect is induced by upregulation of the expression of GCLC, and COX-2, and downregulation of Bcl-2. The modulation of NF-κB by carnosic acid in hepatocarcinoma is mediated by Akt signaling. This was confirmed *in-vitro* and *in-vivo* (130). By modulation of the Akt/mTOR signaling pathway, carnosic acid also prevents proliferation and survival of human gastric cancer cells (131). This inactivation of the Akt/mTOR pathway contributes to the induction of autophagic cell death in hepatoma cells (295). Carnosic acid enhances the apoptosis of human colorectal carcinoma cells via generation of ROS, induction of p53, activation of caspases and modulation of Janus kinase 2 (JAK2)-STAT3/Src-STAT3 signaling pathway (132). ROS generation also promotes anti-tumorigenic signaling and stimulates oxidative stress-induced cancer cell death (273). In human cervical cancer cells, carnosic acid induces ROS production, which phosphorylates the JNK, activates endoplasmic reticulum stress, and induces apoptosis. In addition, a notable decrease in tumor formation was observed in cancer cells xenografted mice after administration of carnosic acid for five weeks (133). The induction of apoptosis by carnosic acid also enhances the effect of tamoxifen in breast cancer cells via caspase-3/TNF-related apoptosis-inducing ligand (TRAIL) activation. The combination of carnosic acid and tamoxifen also led to breast tumor suppression in a mouse xenograft model (134). Carnosic acid also acts in synergy with curcumin to activate the expression of antioxidants (AKR1C2, HO-1) and apoptotic genes (GDF15, PHLDA1, DDIT3) as well as inhibit the cell cycle genes (CDKN2C) (296). Carnosic acid, in combination with fisetin, induces apoptosis in lung cancer cells via

activation of caspase-3 (297). Carnosic acid loaded into transferrin-conjugated liposomes have been reported to mediate apoptosis in liver cancer, both *in-vivo* and *in-vitro,* via upregulating the expression of cleaved PARP, caspase-3 and -9, and downregulating the expression of Bcl-2 (135).

Carnosol

Carnosol **(9)** is a phenolic diterpene which is present in rosemary (*Rosmarinus officinalis*) (68). This molecule has been found to increase the nuclear translocation and accumulation of Nrf2 as well as ARE activity resulting in the induction of phase-II enzymes and the increased expression of the GSH synthesis enzyme subunit GCLC/GCLM (298). Carnosol also enhances HO-1 activity in both mRNA and protein levels by causing nuclear translocation of Nrf2, increasing its binding to ARE and inducing Nrf2-dependent activation of the HO-1 promoter region (299). Being a strong Nrf2 activator, it also induces NQO1 and can modulate other intra and extracellular signaling in addition to activation of Nrf2/HO-1 signaling (300). Carnosol activates the ERK, p38 and JNK pathways with PI3K driven survival pathway in PC-12 cells (301). One study revealed that a carnosol-containing rosemary extract was able to suppress the growth of HCT116 colon cancer cells by upregulating Nrf2 through the protein kinase RNA-like endoplasmic reticulum kinase (PERK)/Nrf2/Sestrin-2 mediated pathway (136). Carnosol can also inhibit EGF-induced epithelial to mesenchymal transition which enables cancer cells to become invasive and undergo metastasis via inhibiting the phosphorylation of ERK (302). Carnosol also protects prostate cancer PC3 cells via modulation of the PI3K/Akt/mTOR and AMPK signaling pathways (137). It has antitumorigenic activity against human colon cancer cells, reducing STAT3 signaling and ROS generation (303). The latter promotes anti-tumorigenic signaling, oxidative stress-induced apoptosis (273), and blocks the growth, invasion and migration of MDA-MB-231, Hs578T, MCF-7, and T-47D breast cancer cells via targeting STAT3 signaling (138). Carnosol has demonstrated a cytoprotective effect against H_2O_2 in HepG2 cells (298). It has also been demonstrated that the activation of Nrf2 in HepG2 cells is caused by increased expression of sestrin2 and MRP2 (139). In stress situations, the sestrin (1–3) family can interact directly with AMPK to maintain genomic integrity and suppress tumorigenesis (304). Carnosol can enhance the effect of curcumin on cancer cells via reducing the phosphorylation of ERK1/2, Akt and STAT3 (302). Although one recent review included *in-vitro* and *in-vivo* studies on the effects of carnosol against cancer (305), this did not include any *in-vivo* work on its role in the Keap1/Nrf2/ARE and interconnected pathways.

Ellagic Acid

Ellagic acid **(10)** is a polyphenol abundant in fruits and nuts, particularly cranberries, raspberries, walnuts and pecans (69).

Ellagic acid increases Nrf2 translocation and HO-1 activity in cells by downregulation of mRNA and Keap1 protein levels (306). This Nrf2/HO-1 activation by ellagic acid modulates Akt and ERK phosphorylation, thereby preventing oxidative stress in HepG2 cells (307). The activation of Nrf2 also suppresses ROS and MDA levels while enhancing GSH and Mn-SOD levels (308). In UVA stimulated HaCaT keratinocytes, ellagic acid induces autophagy by enhancing the expression of γ-GCLC, HO-1, and NQO1 proteins via Nrf2 activation and other signaling pathways, such as ERK, JNK, and PI3K/Akt/mTOR (309). Its antitumor effect against endometrial cancer, via inhibition of PI3K and MMP9 expression, was reported *in-vitro* and *in-vivo* (140). In MDA-MB-231 breast cancer cells, it acts as an anti-angiogenetic agent, limiting the development and migration of cells via inhibition of the PI3K/Akt and MAPK pathway of VEGFR 2. In MDA-MB-231 xenografted animal models, ellagic acid reduced tumor growth via suppressing P-VEGFR2 expression (141). Ellagic acid decreases the proliferation and development of prostate cancer PC3 cells via downregulating the phosphorylated STAT3, ERK and Akt signaling proteins (142). In Mia PACA-2 and PANC-1 human pancreatic carcinoma cells, ellagic acid has an antiproliferative effect, causing apoptosis via inhibition of the NF-κB pathway (143,310). In PANC-1 tumor-bearing mice, it was found to reduce tumor growth via downregulation of COX-2 and NF-κB expression (143). Ellagic acid exerts a hepatoprotective effect against methotrexate-induced toxicity *in-vivo* by upregulating Nrf2 and HO-1 expression and inhibiting the NF-κB signaling pathway and the overproduction and expression of inflammatory factors (311). In T24 human bladder cancer cells, it induces apoptosis via increasing G_0/G_1 phase cell cycle arrest and upregulating p53 and p21 expression (144). In human bladder cancer xenografted animal models, ellagic acid demonstrates notable decrease in tumor growth rate, infiltrative behavior and tumor-associated angiogenesis, with upregulation and downregulation of VEGF-A and VEGFR-2 expression, respectively

(312). In lung cancer, ellagic acid abolishes mitochondrial respiration and tumor growth both *in-vivo* and *in-vitro* via upregulating AMPK and downregulating HIF-1α expression (145).

Apigenin

Apigenin **(11)** is a flavonoid that constitutes with the aglycone moiety of many naturally-occurring glycosides, including apigetrin, vitexin, and isovitexin. It is widely distributed in many plants and vegetables, such as parsley, celeriac, celery, and in chamomile tea (70). It possesses different biological effects including anti-inflammatory, antioxidative, antitumor properties (313).

It protects against oxidative stress through the upregulation of the antioxidant HO-1 enzyme mediated via Nrf2 signaling (146,314). The α, β unsaturated ketone moiety of apigenin interacts with the cysteine residues in Keap1, leading to activation of the Keap1-Nrf2-ARE system (134). Apigenin induces ARE activity, enhances Nrf2 mRNA and protein levels and the expression of HO-1 in HepG2-C8 cells. This ARE activation is mediated through different signaling pathways including MAPK, p38, ERK 1/2 and JNK (315). In human melanocytes, it exerts antioxidative activity via increasing levels of SOD, CAT and GPx enzymes. In another study using melanocytes under hydrogen peroxide-induced oxidative stress, apigenin enhances cell viability, SOD, CAT, and GPx activities and inhibits MDA levels (316). In hepatocellular carcinoma cells, apigenin inhibits cell proliferation and autophagy via suppressing the PI3K/Akt/mTOR pathway (70). Skin carcinogenesis is also prevented by apigenin via restoration of the activation of Nrf2 and enhancing its downstream gene NQO1 as well as decreasing epigenetic proteins, such as DNA methyltransferase (DNMT) and histone deacetylases (HDAC) expression (146). It can also protect hepatocytes from tBHP-induced stress by upregulating HO-1, GCLC, and GCLM gene transcription via the ERK2/Nrf2/ARE signaling pathway (314). Overexpression of Nrf2 can cause chemoresistance and in this regard, apigenin shows Nrf2 inhibiting activity which is enhanced by hyaluronic acid-based nanostructured lipid carriers (NLCs). HAAPG-NLCs significantly decrease Nrf2, multidrug resistance-associated protein 2 (MRP2), HO-1 and Bcl-2 with an increase in Bid mRNA levels, thereby improving the efficacy of docetaxel in lung cancer (147). Apigenin is also effective in doxorubicin-resistant hepatocellular carcinoma cells (317). Several pharmaceutical preparations containing apigenin in combination with other natural products have been reported as useful for preventing or treating cancers (318,319). It can also upregulate the mRNA and protein expression of Nrf2 and its downstream genes via activation of the PI3K/Nrf2/ARE pathway. It exerts its anti-inflammatory effect by suppressing LPS-induced NO, iNOS, and cPLA2 (315). Two different studies conducted on the activity of apigenin against prostate cancer report that it exerts this effect both *in-vivo* and *in-vitro* via inhibiting Akt signaling and inducing apoptosis (148,149). Apigenin also shows anti-colon cancer effects. This has been demonstrated *in-vitro* and on xenografted mice model via inhibition of the m-TOR/PI3K/Akt pathway (150). Furthermore, apigenin has anti-leukemic activity. This has been observed *in-vitro* and in U937 xenografts via inactivation of Akt and activation of JNK expression (151). In cervical cancer, xenograft models suggest evidence for the antitumor activity of apigenin which is able to reverse the abnormal estrogen receptor signal in tumor tissue. The underlying molecular mechanism of this effect is via suppression of the PI3K/Akt/mTOR signaling (152).

Catechin

The polyphenol catechin **(12)** is found in green, white, and black tea *(Camellia sinensis)* (71,72). Green tea contains the highest amount of catechin making up to 25% of its leaf composition (320).

Catechin interacts with the Nrf2 binding site of Keap1 thus suppressing the Keap1-Nrf2 interaction. It increases the ERK1/2 expression, promotes the phosphorylation of ERK1/2, enhances Nrf2 nuclear translocation and increases the expression of Nrf2-dependent genes including GCLC/GCLM, HO-1 and NQO1 (321). In addition, catechin upregulates Nrf2 expression by inactivating the NF-κB signaling pathway (322). This inactivation blocks anti-apoptotic gene Bcl-XL expression and increases apoptosis which contributes to the anticancer activity of catechin (290). Catechin has also been demonstrated to synergize the effects of the anticancer drug 5-FU *in-vitro* (323). The activation of the Keap1/Nrf2/ARE pathway by catechin leads to an antioxidative effect via the upregulation of Gpx, glutathione reductase (GR), and an increase in total sulfhydryl groups associated with high Nrf2 and HO-1 expression (324). Interestingly, one study showed that catechin-derived metabolites (produced by the intestinal microbiota) when combined with curcumin could abrogate VEGF expression and suppress miR-210 and miR-21 oncogenic microRNAs, protecting against cervical cancer (153). In addition, catechin and curcumin exert synergistic activity

against human colon adenocarcinoma HCT 15, HCT 116, and human larynx carcinoma HepG-2 cell lines (154). To the best of our knowledge, no In Vivo studies have been carried out to investigate the cancer protective role of catechin via modulation of Keap1/Nrf2/ARE and interconnected pathways.

Epicatechin

Among four diastereoisomers of catechin, (-)-epicatechin **(13)** is found in green tea, grapes and cocoa (73,74). It has antioxidant and anti-inflammatory activity and is effective against various diseases such as cancer, diabetes, cardiovascular disease, stroke and neurodegenerative disorders (325).

Studies demonstrated that epicatechin increases the nuclear accumulation of Nrf2 by interacting with Keap1, therein upregulating the expression of phase II enzymes, and providing protection against oxidative injury (326). Epicatechin increases GSH levels via activating the Nrf2 pathway and upregulating ARE-mediated HO-1 and NQO1 gene expressions (327). Some studies have demonstrated the anticancer effect of epicatechin. For instance, it induces apoptosis via generating ROS and modulating pro-apoptotic proteins resulting in decreased viability in MCF-7 and MDA-MB-231 breast cancer cells (155). Epicatechin can synergize the anticancer activity of panaxadiol on human colorectal cancer cells (156). The synergistic effect has also been observed on human gastric carcinoma cells where epicatechin, along with (-)-epigallocatechin-3-gallate, exerts cytoprotective activity (157). The exact mechanism behind this activity is not clear, but this might be exerted through modulation of various cell cycle regulatory pathways, including activation of the Keap1/Nrf2/ARE and modulation of the PI3K/Akt and ERK pathways (328). In addition, epicatechin has been shown suppress the PI3K/Akt/mTOR signaling pathway to inhibit the prostate cancer cell migration (158). It can also upregulate ERK1/2 and suppress MAPKs (JNK1/2 and p38) (326), thus impacting on cell proliferation, differentiation, migration, senescence, apoptosis, and inflammation (315). All of the pathways aforementioned are linked with cellular transformation, tumorigenesis, cancer promotion and progression (329). Epicatechin has been demonstrated to reduce liver inflammatory injury by inhibiting the NF-κB activation (73). Epicatechin can also activate this NF-κB pathway in HepG2 cells and this activation is related to ERK, PI3K/Akt and Nrf2 signaling as well (328). One study reported that an epicatechin-rich extract had *in-vitro* and *in-vivo* anti-leukemic activity as it arrested the cell-cycle at the G_0/G_1 phase, activated caspase-3 and -8, increased levels of the anti-inflammatory cytokines IL-10 and IL-4, and suppressed of NF-κB activation (159).

EGCG

(-)-Epigallocatechin-3-gallate or EGCG **(14)** is the predominant polyphenol in green tea. It has antioxidant potential and has been widely studied for its anticancer potential *in-vitro* and *in-vivo* (75).

A study showed that EGCG exerts significant cytoprotection against H_2O_2 by upregulating HO-1, Nrf2 levels in nuclear extracts and ARE-luciferase activity via modulating the Akt and ERK1/2 pathways (330). The Akt and MAPK pathways contribute to anti-apoptotic and growth stimulatory signaling (331). EGCG also regulates ARE-driven antioxidant gene expression through induction of HO-1 and Nrf2 nuclear translocation mostly mediated by modulation of Akt, p38 and MAPK signaling in B lymphoblasts (332). EGCG inhibits the MAPK and PI3K/Akt signaling pathways and modulates the expression of target genes which are associated with induction of apoptosis and cell cycle arrest in cancer cells (333). Moreover, it upregulates the expression of Nrf2 and related antioxidant enzymes (GST, NQO1) as well as reduces DNA binding of NF-κB that inhibits the expression of inflammatory markers, such as monocyte chemotactic protein-1 (MCP-1) and vascular cell adhesion protein-1 (VCAM-1) producing PCB 126-induced inflammatory responses in endothelial cells (334). Another report suggests the same notion regarding the anti-oxidative role of EGCG where they show that prevention of the activation of carcinogens by EGCG is mainly induced by the phase II detoxifying enzymes (335) and thus contributes to cancer chemoprevention (75). It also stimulates caspase-3 activity and induces apoptosis (336). The activation of Nrf2 by EGCG increases the sensitivity of colorectal cancer cells toward radiation therapy, causing autophagy and inhibiting cell proliferation (160). EGCG can increase the activity of chemotherapeutic agents by activating the AMPK pathway and inhibiting COX-2 expression (337). The activation of Nrf2 by EGCG suppresses ROS production and has been reported to exert a cytoprotective effect on pancreatic cells (338). EGCG also reduces ERK activation and activates p38 and JNK, and thus reduces the growth, invasion and angiogenesis in pancreatic cancer cells (339). EGCG is able to suppress multi drug resistance (MDR). It has been reported to reduce Nrf2-mediated etoposide resistance in lung adenocarcinoma cells

(161). It reverses MDR by downregulating the Akt/mTOR pathway and sensitizing MDR cancer cells to chemotherapeutic agents (340). The downregulation of PI3K/Akt/mTOR/HIF-1α by EGCG can also inhibit endometrial tumor angiogenesis (162). EGCG has also been demonstrated to stop tumor growth, proliferation, migration, and angiogenesis in breast cancer cells via modulating the aforementioned pathways (341). EGCG induces apoptosis in estrogen receptor negative MDA-MB-468 breast adenocarcinoma cells (163). The downregulating effect of EGCG on the PI3K/ERK/NF-κB and PI3K/Akt pathways suppresses cancer cell invasion and induces apoptosis, respectively, while modulation of Nrf2 by EGCG causes antioxidant activity and induces apoptosis in breast cancer cells (342). I*n-vivo* studies have revealed that EGCG is most active against breast, colorectal, esophageal, gastric, lung, neural, oral and prostate tumors. These effects are induced via upregulation of Nrf2-UDP glucuronosyltransferase one family, polypeptide A (UGT1A) and VEGF/VEGFR, and downregulation of p-ERK1/2, COX-2, IL-6, and HIF-1α expression (164).

Fisetin

Fisetin **(15)** is a flavonoid found in various vegetables and fruits, including strawberry, persimmon, grape, onion, apple and cucumber (76). Fisetin has anticancer, antioxidant, and anti-inflammatory activity (343).

The mechanism behind its antioxidative activity can be explained by its effect on Nrf2 activity. By dissociating Nrf2 from Keap1, fisetin enhances the accumulation of Nrf2 in the nucleus and increases the upregulation of ARE-regulated downstream genes coding for HO-1, GCLC, GCLM and NQO1 (344). Fisetin has been demonstrated to increase GSH and SOD and reduce inflammatory cytokines release *in-vivo* via activating Nrf2/HO-1 and inhibiting the TLR4/NF-κB pathway, respectively (345). Fisetin also regulates antioxidative mechanisms, such as SIRT1/Nrf2 signaling, and suppresses the activated p-JNK/NF-kB pathway to protect against oxidative stress (346). The Nrf2 mediated upregulation of HO-1 provides cytoprotection from H_2O_2 induced cell injury in human umbilical vein endothelial cells (HUVECs) (347). This Nrf2/HO-1 activation is also responsible for induction of apoptosis and attenuation of liver damage (120). The cytoprotective effect of fisetin is mediated by phosphorylation of ERK, JNK and p38/MAPK pathways (348). These pathways play a central role in cell proliferation, differentiation, transformation, migration and apoptosis (349). The cytoprotection through ERK modulation helps in protecting from cholangiocarcinoma (165). Fisetin induces apoptosis in oral squamous cell carcinoma by inhibition of autophagy (166). This is also seen in MCF-7 breast cancer cells where fisetin induces apoptosis by inhibiting autophagy (350). Fisetin inhibits autophagy by activating PI3K/Akt/mTOR and modulating the AMPK signaling pathway (351). Another report suggests that it ameliorates mammary carcinoma both *in-vitro* and *in-vivo* via inhibiting PI3K/Akt/mTOR (167). It can suppress the phosphorylation of MAPK/ERK/JNK and mRNA levels of pro-inflammatory factors (352). It can eliminate damaged mitochondria in a p62-dependent manner, inhibiting the TLR4/MD2-mediated activation of the NLRP3 inflammasome (353). Fisetin also inhibits inflammation and has a cytoprotective role in nephropathy by blocking of iRhom2/NF-κB signaling (354). In hypoxia/re-oxygenation-treated RAW264.7 cells, fisetin exerts anti-inflammatory activity through modulation of the GSK-3β/AMPK signaling (355). In LPS-stimulated human pulmonary artery endothelial cells, fisetin suppresses iNOS and TNF-α via downregulating p-STAT-1 and NF-κB pathway (356). Through inhibiting this pathway and inhibiting the phosphorylation of ERK1/2 proteins, fisetin exerts anti-inflammatory activity (357). Along with the inhibitory activity toward NF-κB, fisetin upregulates p53 to cause the induction of apoptosis in bladder cancer cells (168). In colon cancer cells, fisetin also induces apoptosis upon modulation of the COX-2 and Wnt/EGFR/NF-κB signaling pathways where it inhibits COX-2 and EGF production (169). Fisetin inhibits proliferation and migration of colorectal cancer cells and induces apoptosis, partially via interfering with signaling pathways related to the cell cycle regulators p21, p27, cyclin D1 and NF-κB p65. Suppression of tumor growth is also observed in mice inoculated with human HCT 116 colorectal cancer cells (170). In prostate cancer cells, fisetin inhibits the PI3K/Akt pathway and induces apoptosis (171). *In-vitro* and i*n-vivo* evidence indicate that fisetin is able to suppress angiogenesis by mediating cell cycle arrest at G_1 and G_2/M phases, reducing cyclin D1 and survivin, enhancing the levels of p53, cleaved caspases-3 and -7 and PARP, and the ratio of Bax to Bcl-2 (358). Fisetin downregulates eNOS, VEGF, iNOS, MMP-2 and -9 expression in A549 lung and DU145 prostate cancer cells. The effect of fisetin in pancreatic cancer via suppression of the PI3K/Akt/mTOR pathway was confirmed *in-vivo* (172). Fisetin causes apoptosis in HeLa cells by ERK1/2-induced activation of caspase-8 and -3. This effect was also confirmed with decreased tumor growth in xenografted mice (173). A recent study suggests evidence

in favor of the anti-colorectal cancer effect of fisetin *in-vivo* and *in-vitro* via downregulation of cyclin D1 and NF-κB and induction of apoptosis (359).

Genistein

Genistein **(16)** is a flavonoid found in soybean seeds and known for its estrogen-like biological activity (77). Genistein has demonstrated activity in various cancer cells, including leukemia, lymphoma, prostate, breast, lung and head and neck cancer cells (360).

Its anticancer effect, along with its antioxidative and anti-inflammatory activity can be attributed to its modulation of Nrf2 signaling. Genistein causes an increase in Keap1 S-nitrosylation with nuclear accumulation and DNA binding of Nrf2, resulting in an elevated level of antioxidant gene HO-1 expression. Genistein has demonstrated its cytoprotective activity against oxidative stress-induced epithelial cells through the activation of Nrf2 pathway and consequent upregulation of HO-1, SOD, CAT, GSH and NQO1 expressions (361). A study reported that the activation of HO-1 and GCLC mRNA and protein expression is mediated via activation of ERK1/2 and PKC/Nrf2 signaling (362). Genistein also activates Nrf2 via modulating PI3K activity, contributing to cytoprotective activity in cerebrovascular endothelial cells (363). The modulation of PI3K/Akt and Nrf2/ARE activity by genistein contributes to the cancer chemopreventive activity of this molecule as these pathways regulate cell cycle progression, transformation, migration and apoptosis (364). Genistein helps prevent prostate cancer by inhibiting the nuclear translocation of NF-κB, its binding to DNA, as well as blocking NF-κB activation by DNA-damaging agents (174). Genistein, in combination with gemcitabine, displays anti-pancreatic cancer activity. This has been evidenced *in-vitro* and *in-vivo* via abolishing NF-κB and Akt expressions (175). Genistein shows anti-inflammatory activity via inhibiting the production of pro-inflammatory mediators, including NOS2, COX-2 and MMPs that are produced following NF-κB activation (365). It can modulate the genes associated with cell cycle and apoptosis by inactivating NF-κB and Akt pathways that affect the cell cycle and apoptosis (360). By inducing apoptosis and inhibiting uncontrolled cell proliferation, genistein prevents the growth of MCF-7 breast cancer cells as well (176). It activates the phase-II UDP-glucuronosyltransferases (UGTs) via SIRT1 activation (366). Active SIRT1 has a biological effect on growth regulation and tumorigenesis and therefore, SIRT1 modulation provides anticancer activity (367,368). Genistein has anti-leukemic activity *in-vitro* and *in-vivo*, inducing ROS and Ca^{2+} generation (177). It mediates apoptosis by G_2/M phase cell cycle arrest, enhances the expressions of pro-apoptotic proteins, including Bax, PARP-cleavage, caspase-9, and -3, and reduces the expression of the anti-apoptotic protein Bcl-2. It sensitizes bladder cancer cells to hydroxycamptothecin *in-vitro* and *in-vivo* via apoptosis and the suppression of NF-κB (178). Genistein has also been reported to enhance the activity of cisplatin on NSCLC *in-vitro* and *in-vivo,* via reduction of Akt and PI3K phosphorylation (179).

Isoorientin

Isoorientin **(17)** is a flavonoid found in different plant species used for edible purposes, like *Phyllostachys pubescens*, *Sasamorpha borealis*, *Eremurus spectabilis*, and *Fagopyrum esculentum (*buckwheat) (78,79). Isoorientin has anti-nociceptive, anticancer and anti-inflammatory activity (369).

It activates Nrf2 signaling and upregulates the expression of Nrf2-mediated antioxidative proteins (GCLC, GCLM, HO-1, NQO1 and Trx-1) and decreases the expression of Keap1 causing its dissociation from Nrf2 (370). This activity helps to exert its antioxidative effect against cell injury. The antioxidative activity of isoorientin has been shown to ameliorate the cisplatin-induced side effects via activating the SIRT1/SIRT6/Nrf2 pathway. Apart from increasing the phase-II detoxifying enzymes, isoorientin also increases GSH levels in the liver and acts as a hepatoprotective agent (371). The activation of phase-II enzymes, specially NQO1 by isoorientin fights against oxidative damage in liver carcinoma and provides cytoprotective activity that is dependent on the PI3K/Akt pathway (79). Isoorientin induces apoptosis in HepG2 cells by modulating the PI3K/Akt pathway as well upon inhibition of Akt phosphorylation (180). Apoptosis in HepG2 cells is also caused via modulation of the MAPK/ERK pathway (372). It also exerts an inhibitory effect on p53 and the PI3K/Akt dependent NF-κB pathway (78). Isoorientin inhibits the expression of inflammatory mediators, like COX-2, TNF-α, IL-6, 5-LO, and IL-1β via NF-κB inhibition (373). Furthermore, isoorientin increases the expression of p-GSK-3β, thereby causing inhibition of GSK-3β and suppression of inflammation (374). Isoorientin has also demonstrated antitumorigenic activity on pancreatic cancer cells by activating the AMPK pathway and decreasing the secretion of VEGF by AMPK (181). In UVB-induced skin carcinogenesis, isoorientin provides protection by its autophagic

action and suppression of JNK pathway activation (182). Isoorientin induces apoptosis in lung cancer cells via modulating the MAPK/STAT3/NF-κB signaling pathways (183), which are all linked with cellular transformation, tumorigenesis, cancer promotion and progression (329). A recent study revealed that isoorientin is effective against oral squamous cell carcinoma *in-vitro* and *in-vivo*. The inhibition of EMT potential via suppression of JAK/STAT3 and Wnt/β-catenin signaling is involved behind this effect (184).

Quercetin

Quercetin **(18)** is a flavonoid found in various fruits, vegetables, and in tea, red wine and medicinal herbs (80). This compound has numerous biological properties including an ability to protect different organs (375).

Quercetin increases Nrf2 mediated transcription and binding activity with ARE, stabilizes Nrf2 and enhances the mRNA and protein expression of Nrf2. It also reduces the level of Keap1 and enhances Nrf2 translocation in the nucleus, causing the activation of Nrf2 regulated antioxidant genes and phase-II detoxifying enzymes (376). The activation of Nrf2 by quercetin plays a vital role for various disease prevention. In liver carcinoma, quercetin provides protection from hepatotoxicity upon activation of Keap1-Nrf2 signaling, causing the dissociation and translocation of Nrf2 as well as induction of the JNK pathway (80). It modulates Nrf2 and induces p38-MAPK signaling and cell death in HepG2 cells by increasing glutathione related enzymes, such as GSH, glutamyl cysteine-synthetase (GCS), Gpx, and GR (377). Quercetin restores SOD and MDA levels via upregulating Nrf2 (378). It activates the phosphorylation of JNK, p38 and PI3K/Akt as well as enhances Nrf2 DNA binding activity (379). In LPS-induced oxidative stress, quercetin attenuates the LPS-mediated inhibition of JNK, ERK and p38 phosphorylation in the MAPK/Nrf2 signaling pathway (380). It also suppresses NF-κB nuclear translocation and expression, causing the downregulation of COX-2 and thus exerting anti-inflammatory activity via Nrf2 activation (381). Quercetin protects from inflammatory liver damage by reducing PI3K/Nrf2-mediated oxidative stress, activating mTOR in autophagy, inhibiting the expression of apoptotic factors and suppressing the NF-κB/TLR/NLRP3 pathway (382). It modulates Nrf2/HO-1 and p38/STAT1/NF-κB signaling pathway by upregulating Nrf2 and inducing HO-1 activity, inhibiting p38 and STAT1 activation and inactivating NF-κB (383). This NF-κB inactivation not only provides quercetin with anti-inflammatory activity but also with a cancer protective role as NF-κB signaling affects cell survival and proliferation, and is linked with carcinogenesis and the response of cancer cells to therapy (290). It shows antigenotoxic effect and prevents DNA damage in human hepatoma cells by blocking the NF-κB pathway as well (185). This effect of attenuating DNA damage also protects colon cancer cells from 1,2-dimethylhydrazine-induced colon cancer (186). Along with vitamin C, quercetin exhibits cytotoxicity against MDA-MB 231 breast cancer cells via reducing the overexpression of Nrf2 and balancing ROS levels (187). This cytotoxic effect of quercetin and vitamin C has also been observed in DU145 and PC3 prostate cancer cells upon decrease in Nrf2 gene expression (188). It has been noted that in some cases it is important to decrease Nrf2 levels because overexpression of Nrf2 causes a marked increase in chemoresistance (384). In combination with kaempferol and pterostilbene, it exerts a synergistic effect on ROS scavenging by activating Nrf2/ARE signaling and increasing the expression of mRNA and protein Nrf2 levels (385). Quercetin also induces apoptosis by modulating the Nrf2 pathway and providing cytoprotection in malignant mesothelioma MSTO-211H and H2452 cells (189). Quercetin has anti-prostate cancer activity *in-vitro* and *in-vivo*. It significantly increases antioxidant enzymes (SOD, CAT, Gpx, GR, and GST), reduces the expression of the anti-apoptotic protein Bcl-2, and enhances the expression of caspase-8. It is able to suppress Akt and ERK levels in prostate cancer-induced rats (190). Studies on different animal models have reported that its cancer protective mechanism is mediated via downregulation of PI3K/Akt, Akt/mTOR and upregulation of JNK/ERK MAPK signaling (386). Another study showed that quercetin could, in addition to its apoptotic effect, enhance the levels of SOD, GSH, and reduce the level of MDA in lung cancer cells (191).

Luteolin

Luteolin **(19)** is a flavonoid present in high concentrations in celery, green pepper, parsley, perilla leaf, chamomile tea and various other fruits, vegetables and medicinal herbs (81). Luteolin has anti-inflammatory, antioxidative, anti-allergic and anticancer activity (387).

It exerts its biological effects by modulating various pathways, such as the Nrf2/ARE, PI3K/Akt and NF-κB signaling (387). Luteolin shows cytoprotective effect by increasing the binding of Nrf2 with ARE followed by an upregulation of its downstream HO-1 mRNA and protein expression via activating the ERK1/2

signaling (388). This cytoprotective effect of luteolin enables it to protect hepatocytes from tBHP-induced oxidative injury by upregulating GCLC and GCLM, intracellular GSH and HO-1 expression via increasing Nrf2 activity (314). Luteolin has shown synergistic activity with metformin on carbon tetrachloride-induced hepatotoxicity by activating Nrf2/ARE signaling and decreasing the release of inflammatory cytokines IL-1β, TNF-α, and IL-6 (389). Luteolin protects against pyroptosis-linked inflammation by suppressing ROS production via Nrf2 activation and inactivation of the NF-κB signaling that is associated with carcinogenesis via the production of inflammatory cytokines (390). Luteolin also shows activity against oxidative cell injury via the activation of Nrf2/ARE that causes the upregulation of Nrf2 downstream genes HO-1, NQO1, SOD, GPx, CAT and enhancement of the eNOS mediated S-nitrosylation of Keap1 (391). Luteolin induces apoptosis and exerts its anticancer effect on colon cancer cells by upregulating Nrf2 via the suppression of DNA methylation, followed by initiation of the interaction between Nrf2 and p53 (192). Luteolin attenuates aflatoxin B1-induced apoptosis in mice by decreasing Bax, Cyt-c, caspase-3 and caspase-9 transcription and upregulating Nrf2 and its downstream protein expressions (HO-1, NQO1, GCLC, SOD1) (392). Another study indicated that luteolin attenuates the proliferation and transformation of HCT116 and HT29 cells upon demethylation of the Nrf2 promoter region, thereby upregulating Nrf2 and its downstream antioxidative products (193). Luteolin has also been reported to induce apoptosis in HT29 cells through Nrf2 modulation (393). Apart from its anticancer potential, luteolin also prevents chemoresistance. It is known that overexpression of Nrf2 causes cancer cell promotion and growth that confers therapeutic resistance toward anticancer drugs (394). Luteolin can inhibit Nrf2 when it overexpresses *in-vivo* and downregulate the Nrf2-regulated NQO1 gene expression (395). For instance, A549 human NSCLC cells show resistance toward anticancer drugs as these cells possess constitutively active Nrf2. Luteolin is able to sensitize these cells toward therapeutic drugs by repressing Nrf2 activation (81). Luteolin inhibits the expression of Nrf2, HO-1 and Cripto-1 proteins which cause breast cancer stemness and thereby enhances chemosensitivity (396). It also inhibits the chemoresistance in human colorectal cells toward oxaliplatin by inhibiting the overexpressed Nrf2 and downregulating NQO1, HO-1 and GSTα1/2 expressions (397). It prevents chemoresistance in breast cancer cells as well, by significantly increasing cancer cell death. Here, luteolin downregulates the expression of HO-1 and MDR1 via blocking the Nrf2 activation in MDA-MB 231 breast cancer cells resistant to doxorubicin (194). Luteolin has activity against human bladder cancer *in-vitro* and *in-vivo* by enhancing TRX1 and reducing ROS levels. The inhibition of mTOR signaling is the major pathway by which luteolin exerts this effect (195). Luteolin has an effect on ER-negative breast tumors and melanoma *in-vitro* and *in-vivo* via induction of apoptosis, as evidenced by a marked reduction in MMP-2 and -9 expression, and inhibition of PI3K and Akt phosphorylation (196,197). In a mouse model of pancreatic cancer, luteolin and gemcitabine synergistically induce apoptosis via abrogating K-ras/GSK-3β/NF-κB signaling, reducing the Bcl-2/Bax ratio, releasing cytochrome C, and activating caspase 3 (198). Luteolin, in combination with paclitaxel, acts synergistically against esophageal cancer *in-vitro* and *in-vivo* by abrogating cell migration and EMT that is associated with suppression of SIRT1 expression, and the ROS/JNK-induced activation of the mitochondrial apoptotic pathway (199). Another study shows that luteolin alone is active against esophageal cancer by inhibiting the PI3K/Akt pathway (200).

Rutin

Rutin **(20)**, also known as rutoside or vitamin P is present in various plants, including asparagus, buckwheat, cherries, plums, oranges, grapes, grapefruit, apricots, apples and tea (82). It possesses antioxidant, anti-inflammatory, antiangiogenic, pro-apoptotic, and antiproliferative effects, all of which may participate in the prevention and treatment of cancer (398).

Studies demonstrated that rutin upregulates the expression of Nrf2 by enhancing the activity of downstream HO-1, NQO-1, GST and Mn-SOD phase-II detoxifying enzymes which repair the oxidative imbalance in cells (399). The activation of Nrf2 in association with the degradation of Keap1 via modulating phosphorylation of PI3K/Akt is a major antioxidative mechanism of rutin (399). This demonstrates the anticancer potential of rutin as ROS imbalance is a key factor affecting apoptosis and autophagy (400). Rutin has been reported to hinder tumor growth in colon cancer cells via inhibition of NF-κB signaling and modulation of MAPK and MAPK activated protein kinase 2 (201). This role of rutin in inactivating NF-κB via p38 along with cell cycle arrest also helps prevent lung (202) and gastric cancer (203). Lung cancer can also be blocked by rutin through modulating TNF-α and GSK-3β expressions, which play a vital role in cell cycle, cell proliferation and apoptosis (204). In case of prostate cancer, rutin upregulates

p53 expression synergistically with 5-FU (205). It also provides protection against breast cancer by modulating Akt/mTOR signaling as well as inducing cell cycle arrest at G_2/M phase via p53 signaling (206). Rutin has been reported to protect liver cells against inflammation via downregulating CCl_4-induced activation of NF-κB, TNF-α and COX-2 (401). It suppresses JNK-mediated autophagy in brain cancer cells as well (207). On the other hand, in leukemia THP-1 cells, rutin enhances autophagy and suppresses inflammation by inactivating NF-κB and reducing TNF-α levels (208). Autophagy is an important process that acts both as tumor generator and tumor inhibitor (402). Rutin has also been demonstrated to protect against oxidative stress and inflammation following bisphenol and dibutyl phthalate exposure through upregulation of Nrf2, SOD, GSH and inhibition of NF-κB activation (403). Rutin, along with ascorbic acid, abrogates UVA-and UVB-induced damage in skin keratinocytes, providing cytoprotective activity via the activation of Nrf2 signaling (404). The *in-vivo* activity of rutin against various cancers has been associated with the suppression of STAT3/NF-κB, Bcl-2, AP-1, p38 MAPK and the activation of the Wnt/β-catenin pathway. Its anticancer effect has also been linked to its inhibition of COX-2, iNOS, TNF-α, and ROS (209,210).

Kaempferol

Kaempferol **(21)** is a flavonoid found in many plant-derived foods like *Aloe vera, Coccinia grandis*, *Moringa oleifera*, broccoli, tea, beans and strawberries (83). Kaempferol exerts diverse biological effects, such as antioxidative, anti-inflammatory, and anticancer with potential uses in diseases, such as diabetes, allergy, osteoporosis, cardiovascular, neurodegenerative and infectious diseases (405).

It increases Nrf2 protein expression leading to the upregulation of its downstream HO-1 gene and an increase in SOD and GSH levels (406). This activation of Nrf2/HO-1 signaling reduces ROS levels and is regarded as the major mechanism behind antioxidative activity of kaempferol (385). Kaempferol also elevates nuclear levels of HO-1 and Nrf2 through attenuation of the cisplatin-mediated phosphorylation of p38, ERK1/2 and JNK (407). In case of pancreatic cancer, kaempferol promotes apoptosis by elevating ROS generation and decreasing transglutaminase-2 (TGM2) mRNA and protein levels (212). Kaempferol has also been reported to exert cytoprotective activity in liver and lung cells via upregulating Nrf2 and increasing CAT, SOD and p38 levels (408). In HepG2 cells, t-BHQ induced phase-II enzymes are dependent on Nrf2 stability and kaempferol can influence this stability (409). Besides activating the Nrf2 pathway, kaempferol also suppresses the activation of NF-κB and reduces the levels of TNF-α and IL-6 which helps to exert its protective effect against cellular damage (410). The reduction in intracellular ROS and inflammatory cytokines can help prevent tumorigenesis and carcinogenesis. It induces apoptosis in human MCF-7, SGC-7901, Hela and A549 cells (378). Kaempferol is a potent inducer of Nrf2 and its downstream NQO1 gene and plays a pivotal role in preventing carcinogenesis in breast cancer cells (411). It increases the activity of phosphatase and tensin homolog (PTEN) and AMPK while decreasing the activation of Akt/mTOR signaling (412). Akt/mTOR is a key signaling pathway involved in tumorigenesis (413) and an imbalance in this pathway is responsible for apoptosis resistance (414). Studies have reported that kaempferol had anti-cervical and colorectal cancer activity via inhibition of PI3K/Akt signaling (213,214). Furthermore, kaempferol inhibits the proliferation of human hepatocellular carcinoma cells via inducing autophagy through the activation of AMPK signaling (211). Kaempferol induces G_1 and G_2/M cell cycle arrest by inhibiting the activity of cyclin dependent kinase 2 (CDK2), CDK4, and Cdc2 in HT-29 human colon cancer cells (415). To combat oxidative injury, kaempferol activates and increases the accumulation of the SIRT1 linked with cellular growth regulation and tumorigenesis (367), as well as inhibits PARP1 that leads to increased Nrf2 expression (416). Kaempferol also shows anticancer activity by inhibiting GSK-3β/Nrf2 signaling as GSK-3β plays a vital role in regulating cell cycle, cell proliferation and apoptosis (405). In ovarian cancer, kaempferol upregulates p53 expression and induces cell cycle arrest at G_2/M phase (417). It also prevents gastric cancer tumor growth *in-vivo* and *in-vitro* via modulating Akt, ERK and COX-2 expressions (215). By modulating these pathways that control cell cycle, growth, and apoptosis, kaempferol affects tumorigenesis. It has been reported to alleviate endothelial cell injury and oxidative stress and induce apoptosis in HUVEC cells by activating AMPK/Nrf2/HO-1 signaling (418). It can also modulate the NF-κB/MAPK and AMPK/Nrf2 pathways to decrease inflammation and oxidative stress (419). Besides inducing activation of Nrf2, kaempferol can also downregulate the excess Nrf2 activation through reduction of Nrf2 mRNA and protein levels along with Nrf2 target genes (NQO1,

HO-1, AKR1C1 and GST). In this way, kaempferol increases ROS accumulation and makes NSCLC cells sensitive to apoptosis which causes abrogation of chemoresistance (216). Kaempferol exerts anti-angiogenic effect *in-vitro* in ovarian cancer via abolishing VEGF secretion, suppressing ERK phosphorylation and NF-κB and cMyc expression, but facilitating p21 expression (217). In NSCLC, kaempferol in combination with radiotherapy was reported to show promising antitumor activity *in-vitro* and *in-vivo* via inhibiting the Akt/PI3K and ERK pathways and activating mitochondrial apoptosis (218). In MCF-7 breast cancer cell xenografted mice, kaempferol inhibits the phosphorylation of insulin receptor substrate 1 (IRS-1), Akt, MAPK/extracellular signal-regulated kinase 1/2, and ERK signaling proteins (219). Additional In Vitro and In Vivo studies indicated that kaempferol had anti-breast cancer activity via inhibiting the PKCδ/MAPK/AP-1 pathway and downregulating MMP-9 expression (220).

Strengths/Limitations of Previous Studies and Suggestions for Future Work

The results of the above studies indicate that the 21 selected dietary polyphenols have a promising cancer protective potential via modulation of Keap1/Nrf2/ARE and other interconnected signaling pathways. Studies, carried out using *in-vitro* and/or *in-vivo* models, showed that these compounds exerted their effects (antiproliferative, antitumorigenic, pro-apoptotic, anti-inflammatory, and antioxidative) in a variety of different cancers. A limited number of *in-vivo* studies were performed to confirm the *in-vitro* findings. Only one clinical trial was conducted to evaluate the effectiveness of resveratrol on patients with prostate, colorectal and breast cancer.

Further studies are required to confirm the cancer protective role of the selected dietary polyphenols. In particular, the cancer protective role of polyphenols, such as methyleugenol, carnosol, and catechin, has yet to be studied *in-vivo*. In addition, further work should be focused on designing rigorous controlled clinical trials to establish whether the consumption of such polyphenols has an impact on the incidence and progression of cancers in humans. These compounds may prove to be particularly useful as alternative options for patients with pre-neoplastic lesions, early-stage cancers, as well as in end stage disease where there is enhanced drug resistance.

Authors' Contributions

M.A.I. and M.M.M. were responsible for literature analysis and curation, drafting the final manuscript and drawing the figures. A.U.N. and M.A.A.F were responsible for literature curation, initial drafting of the manuscript and drawing the figures. M.A.S. was responsible for conceptualization, literature searching, revision and supervision. V.S. critically revised the manuscript and was responsible for drafting the final manuscript. All authors have read and approved the submitted version of the manuscript.

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