Review

Food bioactives, apoptosis, and cancer

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Apoptosis interchangeably referred to as programed cell death is a key pathway for regulating homeostasis and morphogenesis of mammalian cells and is connected with several diseases, in particular, cancer. It is widely believed that misregulation of this pathway leads to the development of cancer. Reflecting this knowledge, the mechanism of action for many currently used anticancer agents were specifically targeted to regulate the apoptotic pathway further stressing the role of programed cell death in maintaining normal homeostasis. Another widely accepted concept is the consumption of a variety of colorful foods with strong antioxidant properties. These dietary components also referred to as bioactives would help maintain a healthy body. Although for many of these bioactives exact nutritional benefits are not yet well defined, there is demonstrated scientific evidence suggesting a role for them in cancer prevention. This review summarizes the current knowledge of food bioactives that act through the signaling pathway inducing programed cell death, thus providing the evidence for these substances in cancer prevention.

Keywords: Apoptosis / Cancer / Death receptor / Food bioactives / Mitochondrial

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1 Introduction

Cancer development, a dynamic and long-term process, involves many complex factors with stepwise progression ultimately leading to an uncontrolled spreading and growth of cancerous cells throughout the body called metastasis. The three critical steps in this process for several types of human cancer formation are initiation, promotion, and progression. Epidemiological studies have provided convincing evidence that dietary factors can modify this process. Laboratory research has further demonstrated that the effectiveness of a number of bioactive dietary components collectively referred to as natural products, have the ability to prevent cancer [1] and other chronic diseases [2, 3]. In addition, many food constituents with yet undefined nutritional benefits have been found to possess antimutagenic and anticarcinogenic properties [4]. Such promising research provides a strong support for the acceptance in the future of food bioactives as chemopreventive agents.

Apoptosis is considered an emerging mechanism by which food bioactives could be exerting their anticancer properties as number of natural substances have induced apoptosis in malignant cells *in vitro* [4, 5]. The immense importance of this critical observation becomes obvious specifically when noticing the mechanism of action through which the anticancer drugs or cancer chemopreventive agents induce their effect. A key mechanism of action for these synthetic agents is through the induction of apoptosis. Thus, apoptosis could be an important mechanism through

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Abbreviations: AIF, apoptosis-inducing factor; **CHOP,** CCAAT/enhancer-binding protein (CEBP) homology protein; **DIABLO,** direct inhibitor of apoptosis protein (IAP) binding protein with low p*I*; **DR,** death receptor; **ERKs,** extracellular signal-regulated protein kinases; **GADD153,** growth arrest and DNA damage 153; **GSH,** glutathione; **IAP,** inhibitor of apoptosis protein; **JNK,** c-Jun NH2-terminal kinases; **MAPK,** mitogen-activated protein kinases; **MMP,** mitochondrial membrane potential; **NF-κB,** nuclear factor κB; **5-OH-HxMF,** 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone; **PEITC,** phenethyl isothiocyanate; **PI3K,** phosphatidylinositol 3-kinase; **ROS,** reactive oxygen species; **Smac,** secondary mitochondria-derived activator of caspase; **TNF,** tumor necrosis factor; **TRAIL,** TNF-related apoptosis-inducing ligand

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which natural substances could be exerting its anticancer properties [6, 7].

Chemoprevention, a relatively new and promising strategy to prevent cancer, is defined as the use of natural and/or synthetic substances to block, reverse, or retard the process of carcinogenesis. We have suggested that, food contains bioactive substances with antipromotion and tumor-killing abilities. Further, the phytochemical-induced apoptosis may result from the combined or synergistic actions of a mixture of bioactives found in the diet. The purpose of this review is to discuss the process of apoptosis and the potential effect of food bioactives on this process.

2 Biochemical pathways for apoptosis

Apoptosis, a form of programed cell death, plays a critical role in both development and tissue homeostasis. It is defined as a type of cell death, involving the concerted action of a number of intracellular signaling pathways, including members of the caspase family of cysteine proteases, stored in most cells as zymogens or procaspases [8]. This definition distinguishes the apoptotic process from other forms of cell death, such as autophagy, oncosis, and necrosis [9–12]. Typically, apoptosis is also a gene-directed form of cell death with well-characterized morphological and biochemical features, which is characterized by cell shrinkage, membrane blebbing, chromatin condensation, and formation of DNA ladder with multiple fragments caused by internucleosomal DNA cleavage [13]. Proteolytic cleavage of procaspases is an important step leading to a caspase activation, which in turn is amplified by the cleavage and activation of other downstream caspases in the apoptosis cascade [14, 15]. The two main apoptotic pathways, the death receptor (DR) (extrinsic) and mitochondrial (intrinsic) pathways are activated by caspase-8 and caspase-9, respectively (Fig.1). First is the interaction of a cell surface receptor, such as Fas, tumor necrosis factor receptor (TNFR), DR3, DR4, or DR5, with their ligands. Activation of DR (Fas) by crosslinking with their natural ligands (Fas ligand) induces receptor clustering and formation of a death-inducing signaling complex (DISC). The complex recruits procaspase-8 *via* the adaptor molecule Fas-associated death domain protein (FADD), resulting in the activation of caspase-8. Activated caspase-8 directly cleaves and activates caspase-3, which in turn cleaves other caspases [16–18]. Caspase-8 is recruited as a DISC only when DR such as Fas or the TNFR binds to specific multimeric ligands. Second is the participation of mitochondria, which for most forms of apoptosis, is a response to cellular stress, loss of survival factors, and developmental cues [19, 20]. Caspase-9 is activated when Cytochrome *c* is released into cytoplasm from the mitochondrial intermembranous space. Activated caspase-8 and caspase-9 activate executioner caspases, including caspase-3, which in turn cleave a number of cellular proteins that include structural proteins, nuclear proteins, cytoskeletal proteins, and signaling molecules [14]. Moreover, the mitochondrial pathway is regulated by the Bcl-2 family of proteins, including antiapoptotic proteins such as Bcl-2 and Bcl-X_L and proapoptotic proteins such as Bad, Bid, Bim, Bax, and Bak [21]. Recent studies of the ER as a third subcellular compartment containing caspases were implicated in apoptotic execution induced by ER stress [22–24]. The ER stress-induced cell death modulator is a CCAAT/enhancer-binding protein (CEBP) homology protein (CHOP)/growth arrest and DNA damage 153 (GADD153), known as CHOP, is a member of the CEBP family of transcription factors [25]. Expressed at low levels in proliferating cells, it is strongly induced in response to stresses that result in growth arrest or cellular death, including oxidant injury, DNA damaging agents such as peroxynitrite, UV radiation, anticancer chemotherapy, and ER stress [25, 26]. Recent studies suggested that, GADD153 plays a central role in the apoptosis-induction by overexpression of GADD153, of vector-transfected cells, including the dephosphorylation of the proapoptotic protein Bad and downregulation Bcl-2 expression. In contrast to necrosis, no inflammatory reaction results upon apoptosis [25].

A recent study suggested that mitogen-activated protein kinases (MAPKs) include stress-activated protein kinases such as c-Jun NH2-terminal kinases (JNK) and p38 plays important role in triggering apoptosis in response to various cellular stressors including oxidative stress. Bcl-2 has been reported to be phosphorylated by JNK in response to different stimuli [27]. The phosphorylation of Bcl-2 has been described as an important step from microtubule damage to apoptosis [28]. Furthermore, Bid is believed to be relatively inactive in the cytosol until activated by proteolytic cleavage by caspase-8. However, the apoptotic pathways in which Bid plays a role are not yet fully characterized. Recent studies suggested that Bid is phosphorylated by DNA-damage kinase ataxia-telangiectasia mutated (ATM) and may play an important role for S phase arrest [29, 30].

In many cells, survival or death depends on the altered expression level of death inhibitor to death promoter. Furthermore, it appears that a range of molecular affinities exists, which controls the interactions between family members, such as Bcl-2 (or Bcl-X_L) enabling Bax to promote cell survival or Bax homodimer formation to promote cell death [31, 32]. Current evidence suggests that, Bcl-2 acts as upstream of caspase-3 activation at the level of Cytochrome *c* release to prevent apoptosis [33]. It has been shown that, the Bcl-2 and Bcl-X_L of mammals can be converted into potent proapoptotic molecules when they are cleaved by caspases, resulting in accelerated cell apoptosis [33, 34].

Several observations have established a role for oxidative stress in apoptosis. Oxidative stress is defined as a disturbance in the prooxidant/antioxidant balance, resulting in potential cell damage [35]. Intracellular accumulation of

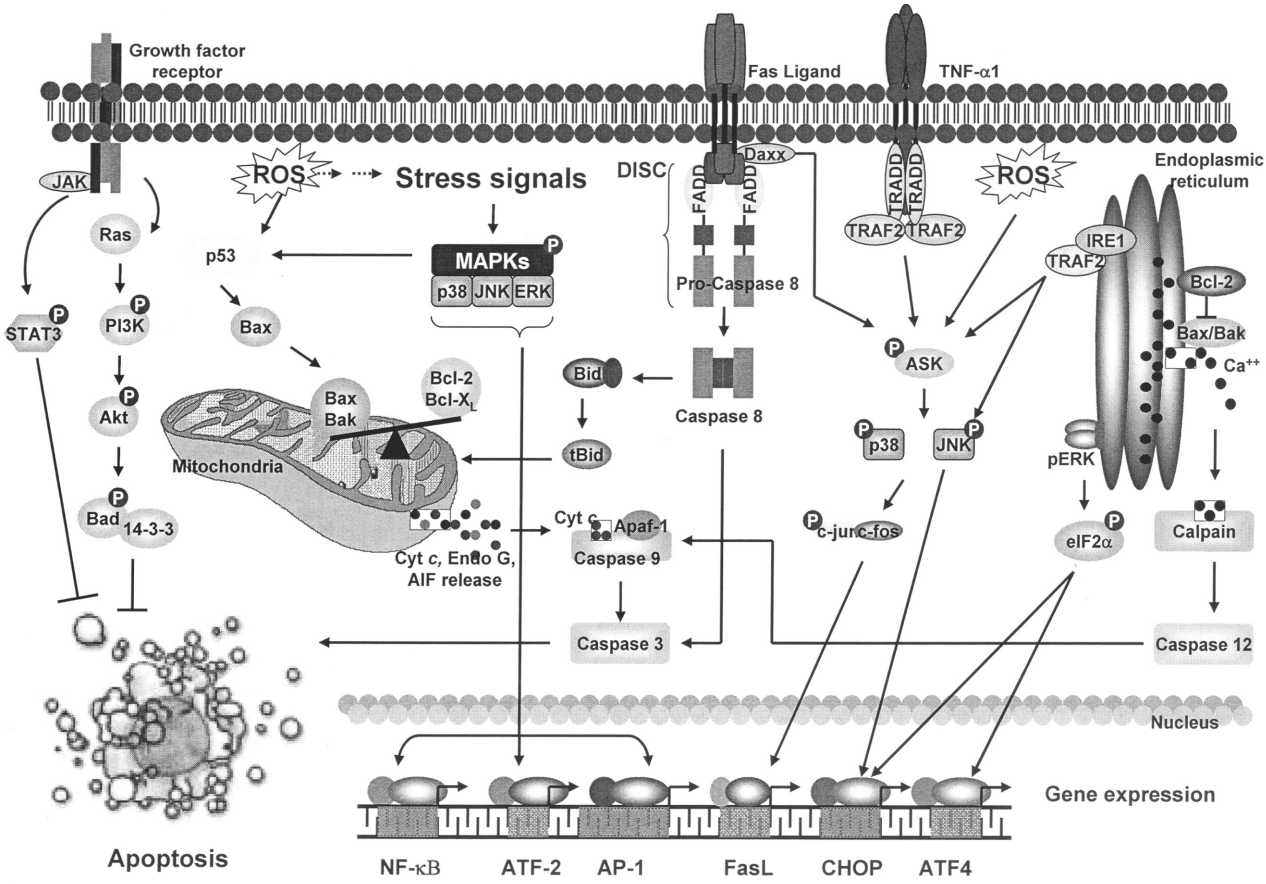

Figure 1. Molecular pathways leading to apoptosis. The signaling pathways leading classical apoptosis involve caspase-activated cascades ultimately leading to activation of executive caspase-3. Depending on the type of stimuli and cell type involved, the apoptotic response is set in motion by an extrinsic pathway initiated by ligation of trnasmembrane DR (Fas, TNF receptor) to activate membrane following the activation of caspase-8 by activation of a DR or by an intrinsic pathway requires disruption of the mitochondrial membrane and the release of mitochondrial protein such as Cytochrome *c*, Engo G, and AIF into cytoplasm. The ER as a third subcellular compartment inducing the activation of calpain and caspase-12, and CHOP. ROS and stress signals elicited by food bioactives regulated the proapoptotic proteins and cellular signaling triggers apoptotic pathways. Food bioactives can also block growth factor-meditated antiapoptotic signals.

reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), hydroxyl radical ($^\bullet$OH), and peroxy radical ($^\bullet$OOR), can arise from normal metabolic processes or toxic insults. As protection against increased levels of ROS, referred to as oxidative radical stress, cells possess several antioxidants, or reductants, that maintain the intracellular redox environment in a highly reduced state. An example is superoxide dismutase (SOD) that converts O_2^- into H_2O_2, and then the H_2O_2 generated is degraded to H_2O by several cellular enzymes. Nonenzymatic defenses include glutathione (GSH), a major cellular reductant found in all eukaryotic cells. Depletion of GSH pools is suggested to be a part of cell death effector machinery, and accompanies ROS production during apoptosis in relevant systems [33].

3 Food bioactives

Plant-based foods, such as vegetables, fruits, and whole grains, which contain significant amounts of bioactive phytochemical, may provide desirable health benefits beyond basic nutrition to reduce the risk of chronic disease and the process of carcinogenesis [36]. The National Cancer Institute of the United States has identified approximately 40 plant-based foods that exert cancer-preventive effects, including turmeric, green tea, red wine, ginger, soybean, cabbage, and cauliflower [37]. Phytochemicals can be classified as phenolics, carotenoids, alkaloids, organosulfur compounds, and terpenoids (Table 1). In general, the antioxidant potential of phytochemicals have been well-documented [36], however, phenolics and carotenoids have been studied the most. The major chemical structures of phyto-

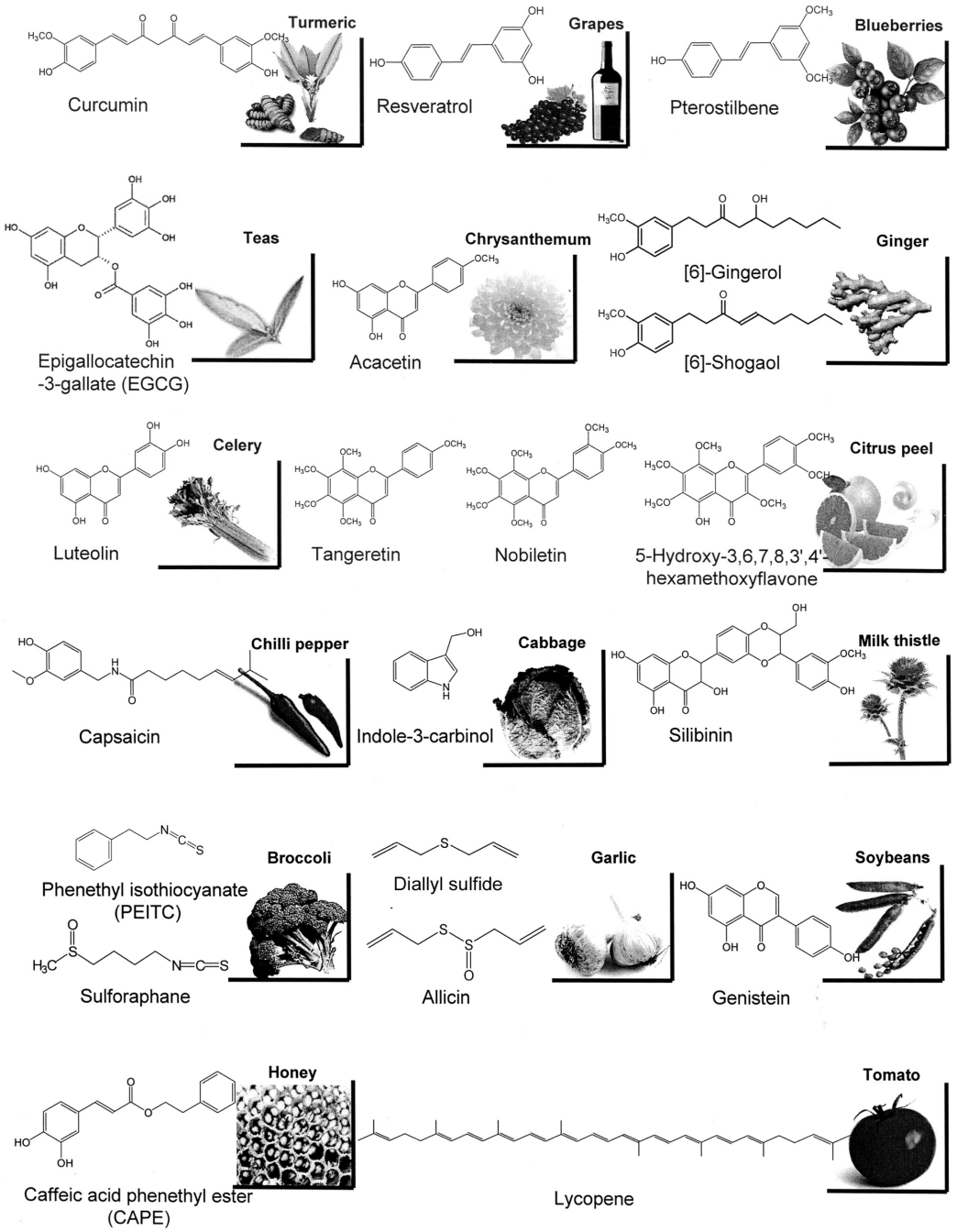

Figure 2. Representative food bioactives and their sources.

phenolic compounds belong to the flavonoids are found in fruits, vegetables, and medicinal plants. These compounds are important in contributing flavor, color, and taste to many fruits and vegetables. They are also important for a normal growth, development, and defense of a plant [38]. The flavonoids mainly consist of flavonols, flavones, flavanols, flavanones, isoflavonoids, and anthocyanidins and their glycosides. Flavonoids are ubiquitous in edible fruits, leafy vegetables, roots, tubers, bulbs, herbs, spices, legumes, tea, coffee, and red wine [39]. Phenolic acids, the other major phytochemicals can be subdivided into two major groups, hydroxybenzoic acids and hydroxycinnamic acids (Table 1). Carotenoids are widespread pigments and have also received substantial attention because of both their provitamin and antioxidant roles. The terpenoids are a class of secondary plant metabolites that are lipophilic in nature and represent the largest and most diverse class of plant compounds. Some important plant terpenoids in food components are limonene from citrus, myrecene from bay leaves, and menthol from peppermint [40]. Figure 2 shows

Table 1. Classification of dietary phytochemicals

Groups			Compounds
Carotenoids	–	–	β-carotene, lycopene, lutein
Phenolics	Phenolic acids	Hydroxybenzoic acids	Gallic acid
		Hydroxycinnanmic acids	Caffeic acid, Ferulic acid
	Flavonoids	Flavonols	Querectin, kaempferol
		Flavones	Apigenin, luteolin
		Flavanols (Catechines)	Catechin, epicatechin, epigallocatechin-3-gallate (EGCG)
		Flavanones	Naringenin, silibinin
		Anthocyanidins	Cyanidin
		Isoflavonoids	Genistein, daidzein
	Stibenes	–	Resveratrol, pterostilbene
	Coumarins	–	Esculetin
Alkaloids	–	–	Caffeine
Organosulfur compounds	–	–	Allicin, PEITC, sulforaphane
Terpenoids			Limonene, myrecene, geraniol, menthol

the selected chemical structures of representative food bioactives that have been shown to induce apoptosis. The cellular and molecular events affected by these bioactives including the intrinsic, or mitochondrial-mediated and the extrinsic, or DR-mediated machineries. In addition to mitochondria, accumulating evidence suggests that other organelles, including the ER, lysosomes, and the Golgi apparatus, are also major points of integration of proapoptotic signaling or damage sensing, and inducing apoptosis (Fig.1) [41, 42]. Table 2 illustrates various food bioactives that have been reported to induce apoptosis in cancer cells.

4 Effect of food bioactives on the mitochondrial-mediated pathway

Many food bioactives induce apoptosis through the intrinsic pathway, whereby, the death stimulus activates a signaling cascade triggering mitochondrial outer membrane permeabilization and release of proapoptotic factors including Cytochrome *c*, endonuclease G, secondary mitochondria-derived activator of caspase (Smac)/direct inhibitor of apoptosis protein (IAP) binding protein with low p*I* (DIABLO), high-temperature requirement protein A2 (HtrA2), and apoptosis-inducing factor (AIF) [43]. The mitochondrion is also a pivotal organelle for the induction of apoptosis *via* mitochondrial fission and fusion [44]. Some of these proteins are now known to contribute to the activation of caspases either through the apoptosome or by binding to IAP. Lycopene, a carotenoid rich in tomato, can induce the release of Cytochrome *c* from mitochondria in human prostate cancer cells [45]. Capsaicin, a phenolic compound, from chili pepper induces a rapid increase in ROS followed by a subsequent disruption of the mitochondrial membrane potential (MMP) in transformed cells [46]. In our laboratory, we have demonstrated that luteolin, in celery; acacetin, in chrysanthemum; 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (5-OH-HxMF), in citrus peel; and curcumin, in turmeric can depolarize the mitochondria of human cancer cells, induce Cytochrome *c* release, caspases activation, and ultimately induce apoptosis [47 – 50]. Conversely, normal cells are largely resistant to the induction of apoptosis by 5-OH-HxMF [49]. Because most tumor cells grow relatively rapidly, the most effective apoptosis-inducing agents are those that interrupt the cellular mitogenic signals. These findings suggested that food phytochemicals can induce apoptosis at a limited window of doses since the generation of ROS and blocking the cellular signal transduction in tumor cells but not in primary culture cells. In cancer chemotherapy, a way of stimulating apoptosis in the malignant cells would be therapeutically valuable. We have also demonstrated that pterostilbene, a stilbene in blueberry can induce apoptosis. The results showed that pterostilbene caused apoptosis by loss of MMP, Cytochrome *c* release and caspase-3 activation, and DNA fragmentation factor (DFF-45) and poly(ADP-ribose) polymerase (PARP) cleavage in human gastric carcinoma AGS cells [51]. Genistein, an isoflavone from soybeans, induced MMP change and ER stress in human hepatocellular carcinomas [52]. Epigallocatechin gallate depolarizes and targets mitochondria signaling transduction pathway in human cancer cells [53, 54]. Dietary ginger constituents, gingerols and shogaols, induced mitochondrial transmembrane potential alteration, Cytochrome *c* release in human leukemia and hepatoma cells [55, 56]. The garlic compounds, diallyl sulfide induced apoptosis by mitochondria-mediated cell death is associated with ROS generation and regulated by Bax/Bak but independent of Bcl-2 or Bcl-X_L [57], and allicin induced apoptosis mediated by mitochondrial release of AIF [58]. Phenethyl isothiocyanate (PEITC), an isothiocyanates in cruciferous vegetables, can induce cell death in PC-3 cells was associated with disruption of the MMP, release of apoptogenic molecules (Cytochrome *c* and Smac/DIABLO) from mitochondria to the cytosol [59].

Table 2. The possible mechanisms of food bioactives modulate apoptosis

Food bioactives		Proposed mechanisms	References
Carotenoids	Lycopene	Downregulate pAkt and pBad; modulate p53, Bcl-2, Bax, Bim, and caspases activation; induced Cytochrome *c* release	[49]
Phenolic acids	CAPE	Downregulate cyclin D1, c-myc, and b-catenin; alter IAPs; induce p53, Fas, Bax, and activation of caspases	[65–67]
Flavonoids	Luteolin	Downregulate ERK and Akt; modulate TNF-induced NF-κB pathway; cleavage of Bcl-2 family; activate caspases and induce Cytochrome *c* release; modulate mitochondria translocation of Bax/Bak and activation of JNK	[51, 71, 78]
	Genistein	Sensitizes TRAIL-induced apoptosis; interaction of ER stress and alter mitochondria insult; inhibit NF-κB and Akt activation; downregulate Bcl-2 and activation of caspase-3; mediate calpain-caspase 7 and ASK1-p38 cascade; increase Ca^{2+} release from ER; activate calpain and caspase-12	[56]
	Silibinin	Inhibits constitutive activation of Stat3; activate p53-caspase 2 pathway; downregulate surviving, Akt and NF-κB; modulate Bcl-2 family protein and CDKI-CDK-cyclin cascade	[79, 80]
	Acacetin	Upregulation of Fas and FasL, p53, p21, and Bax; increase ROS production and alter mitochondrial transmembrane potential; activation of caspases	[52]
	5-Hydroxy-3,6,7,8, 3′,4′-hexa-methoxy-flavone	Increase in concentration of intracellular Ca^{2+}; depletion of the ER Ca^{2+} stores; modulation of mitochondrial function; increase ROS production; Upregulate Bax and activation of caspases cascade	[53]
	EGCG	Downregulate survivin and AKT kinase activity; modulate Bcl-2 family protein; Inhibit ERK and PI3K/Akt signaling; activate Fas and caspases cascade	[57, 58, 72, 81]
Stilbenes	Resveratrol	Modulate ERK activation and inhibit pS6 ribosomal protein expression; activation of p53; depletion of Ca^{2+} and promotes MPT opening; modulate pAkt and caspase-9	[64, 82]
	Pterostilbene	Active Fas/FasL; induce GADD153 and casapses cascade; increased p53 and p21; decrease cyclin proteins and pRb; alter mitochondrial transmembrane potential	[55]
Polyphenol or monophenol	Curcumin	Increase in Bax/Bcl-2 ratio; induced Cytochrome *c* and Smac/DIABLO release; inhibit NF-κB and PI3K/Akt signaling; downregulate EGFR expression and ERK activity; increase production of ROS add Ca^{2+}	[54, 68, 83]
	[6]-Gingerol	Inhibit Bcl-2 expression; increase TRAIL-induced caspase-3/7 activation; inhibit TRAIL-induced NF-κB activation; decrease cyclin A and CDK expression	[56, 69]
	[6]-Shogaol	Increase ROS production and depletion of intracellular GSH contents; alter mitochondrial transmembrane potential; medicate p38 MAPK, p-SAPK/JNK, and STAT3 activation	[60, 77]
	Capsaicin	Alter Ca^{2+} influx and mitochondrial transmembrane potential; activate p38 MAPK and caspase-3; modulate Bcl-2/Bax	[50, 76]
Organosulfur compounds	Diallyl sulfide	Alter mitochondrial transmembrane potential; downregulate Bcl-2 and Bcl-X_L; activate p38 and ERK; decrease intracellular GSH	[61]
	Allicin	Induce AIF release from mitochondria; activation of caspases cascade	[62]
Isothiocyanates	Sulforaphane	Sensitize TNF-related apoptosis; downregulate ERK and Akt; decerase IAP family proteins and increase Apaf-1 expression; inhibit NF-κB translocation; activate calpain and caspase-12	[7]
	PEITC	Induced Cytochrome *c* and Smac/DIABLO release; increase ROS production and alter mitochondrial transmembrane potential; inhibit ERK, Akt, and c-myc; increase transcriptional activity of AP-1	[63, 84]

5 Effect of food bioactives on the DR-mediated pathway

DRs are activated by extracellular ligands such as Fas ligand (FasL, also called CD95L/Apo1L), tumor necrosis factor-α (TNF-α), and TNF-related apoptosis-inducing ligand (TRAIL). Their cognate receptors belong to the TNF receptor super family. Acacetin (5,7-dihydroxy-4′-methoxyflavone), present in safflower seeds, plants, flowers, and *Cirisium rhinoceros*. Nakai has antiperoxidative, anti-inflammatory, antiplasmodial, and antiproliferative activities by inducing apoptosis and blocking the progression of

cell cycles [60]. In our laboratory, we have found that acacetin caused significant upregulation of Fas and FasL [48]. Pterostilbene (*trans*-3,5-dimethoxy-4′-hydroxystilbene), a dimethyl ether analog of resveratrol, isolated from *Vaccinium* berries was found to have a cancer chemopreventive activity [61]. We have recently shown that pterostilbene induced apoptosis through activating the caspase cascade *via* the mitochondrial, and Fas/FasL pathway, GADD expression in human gastric carcinoma AGS cells [51]. Resveratrol has been shown to trigger CD95 signaling dependent apoptosis in human tumor cells [62]. Caffeic acid phenethyl ester (CAPE) induced apoptosis through Fas activation with induction of p53, Bax, activation of caspases, and downregulated cyclin D1, c-myc, and β-catenin in human cancer cells [63–65]. Recent studies demonstrated that curcumin differentially sensitizes malignant glioma cells to TRAIL-induced apoptosis [66]. 6-Gingerol, a phenolic alkanone isolated from ginger, facilitated TRAIL-induced apoptosis by increasing TRAIL-induced caspase-3/7 activation in gastric cancer cells [67]. Treatment with a subtoxic concentration of sulforaphane significantly sensitized TRAIL-resistant A549 cells to TRAIL-mediated apoptosis [68]. Luteolin, a naturally occurring flavonoid commonly found in some medicinal plants, sensitize lung cancer cells to TNF-induced apoptosis through suppression of nuclear factor κB (NF-κB) *via* accumulation of ROS and potentiation of JNK to increase apoptosis induced by TNF [69]. Cotreatment with EGCG and TRAIL synergistically induced apoptosis in human cancer cell lines [70].

6 Effect of food bioactives on the cellular signaling of apoptosis

MAPKs signaling cascades include extracellular signal-regulated protein kinases (ERKs), JNKs/stress-activated protein kinases (SAPKs), and p38 kinases, were involved in apoptosis induced by a variety of different stimuli, such as genotoxic stress and Fas (Apo-1/CD95) [71]. The phosphorylation of MAPK translocation to the nucleus then phosphorylated numerous substrates, including the transcription factors AP-1, ATF-2, and NF-κB. The ERKs transmit signals initiated by growth promoters, including EGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) which can promote cell growth. In contrast, the phosphatidylinositol 3-kinase (PI3K)-AKT pathway has been shown to inhibit apoptosis in most cell types [72]. Inhibition of PI3K-AKT might contribute to cell death through modulation by dietary bioactives [73]. Many food bioactives can induce apoptosis *via* interruption cellular signaling. Capsaicin, 6-shogaol, significantly activate p38 MAPK and JNK1 [74, 75]. Luteolin, silibinin, EGCG, resveratrol, curcumin, sulforaphane, and PEITC induced apoptosis through modulate PI3K-AKT and ERK pathways [68, 76–82]. We have recently shown that 5-OH-HxMF, a citrus flavonoid, induced apoptosis through ROS production, GADD153 expression, and caspase activation in human leukemia cells [49]. These results have significant applications as potential chemopreventive and chemotherapeutic agents.

7 Conclusions

Accumulating evidence supports the notion that a combination of food bioactives is more effective than treatment with single dietary component. Strong epidemiological evidence suggests that regular consumption of fruits and vegetables can reduce cancer risk. Food bioactives offer a great potential in the fight against human cancer by inhibiting the carcinogenesis process through cell defensive and apoptotic machineries. Apoptosis is a more complex process involving intrinsic and extrinsic pathways with numerous specific targets. Accumulating evidence clearly indicates that apoptosis is a critical molecular target for food bioactives for chemoprevention of cancers [83]. To block the initiation of carcinogenesis, enhancement of the detoxifying and antioxidant enzyme system for efficient neutralization and elimination of endogenous or exogenous carcinogenic species provides a good starting point, particularly for the high-risk populations exposed to environmental carcinogens. With regard to the latter stages of carcinogenesis, induction of apoptosis and cell cycle arrest in precarcinoma and carcinoma cells is an attractive goal for many dietary antiproliferation agents. Ultimately, to successfully convert a potent food bioactive to a clinically viable drug will require detailed consideration of *in vivo* pharmacokinetics, intermediate biomarkers and targeted patients, or healthy populations, in addition to the potential combination of mechanistically different chemopreventive compounds to enhance efficacy and reduce toxicity. Therefore, it is reasonable for scientists to identify the food bioactive compounds responsible and hope to find the magic bullet to prevent human cancers. Clearly more research is needed to understand the underlying molecular mechanisms of action of the food bioactives. A clear understanding in this area will provide impetus for future developments in basic and applied medicine, not only in cancer chemoprevention, but also in other diseases such as cardiovascular, inflammation, and neurological disease. Importantly, it will also enhance our understanding of the overall potential health benefits of these compounds, which are consumed abundantly in our daily diet.

The authors have declared no conflict of interest.

8 References

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