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REVIEW ARTICLE

Dietary phytochemicals as the potential protectors against carcinogenesis and their role in cancer chemoprevention

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Abstract

Health-threatening consequences of carcinogen exposure are mediated via occurrence of electrophiles or reactive oxygen species. As a result, the accumulation of biomolecular damage leads to the cancer initiation, promotion or progression. Accordingly, there is an association between lifestyle factors including inappropriate diet or carcinogen formation during food processing, mainstream, second or third-hand tobacco smoke and other environmental or occupational carcinogens and malignant transformation. Nevertheless, increasing evidence supports the protective effects of naturally occurring phytochemicals against carcinogen exposure as well as carcinogenesis in general. Isolated phytochemicals or their mixtures present in the whole plant food demonstrate efficacy against malignancy induced by carcinogens widely spread in our environment. Phytochemicals also minimize the generation of carcinogenic substances during the processing of meat and meat products. Based on numerous data, selected phytochemicals or plant foods should be highly recommended to become a stable and regular part of the diet as the protectors against carcinogenesis.

Keywords Carcinogens · Dietary phytochemicals · Antioxidant · Scavenging effect · Detoxification · Metabolic activation · Chemoprevention

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Introduction

Malignant diseases that are associated with poor clinical outcome are highly actual topic of cancer research [1–6]. Humans are continuously exposed to chemicals, which are associated with mutagenic and/or carcinogenic properties in experimental systems. An exposition to these compounds is mediated endogenously as products of metabolism or pathophysiological state or they may arise exogenously via their presence in the air, water, food or other sources [7, 8]. Therefore, exposure to environmental, occupational and dietary carcinogens is considered to be a risk factor for malignancy and thus contributes to the increase in cancer prevalence [9]. Carcinogens are associated with DNA damage including single- or double-strand breaks, covalently bound DNA chemical adducts, DNA–DNA or DNA–protein crosslinks or oxidative-induced lesions [10]. Consequently, lifestyle factors such as diet or tobacco add to human exposure to chemical carcinogens [8]. Additionally, protein-rich food cooked at high temperatures is a major source of heterocyclic aromatic amines (HAAs) which are associated with cancerogenesis. Moreover, both polycyclic aromatic hydrocarbons (PAHs) and nitrosamines are associated with food processing but they are primarily generated by the use of tobacco products [8, 9]. Despite the hazardous exposure of various chemicals in our environment, diet rich in fruit and vegetable is a good source of chemopreventive phytochemicals. Phytochemicals possess protective ability against carcinogen exposure via various mechanism including antioxidant, detoxifying and free radical scavenging activity. Moreover, phytochemicals modulate proliferative and apoptotic pathways of cancer cells [11, 12]. Importantly, phytochemicals as regulators of epigenetic mechanisms are also highly implicated in the cancer chemoprevention [13–15].

Aim of the study

We provide a comprehensive review concerning the effects of phytochemicals in the exposure of selected carcinogens appearing in a large extent in the human–environment. Accordingly, a representative of each group of chemical carcinogens was chosen to be analyzed in relation with potential intervention by chemoprevention with dietary phytochemicals. In this regard, we have focused on the abundantly occurred and environmentally/clinically relevant chemical carcinogens—2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), benzo(a)pyrene (B[a]P) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN). Considering the cross section of current predominantly experimental studies, we emphasize beneficial activity of phytochemicals against carcinogen-related genomic alterations in cells.

Source of the data

Data were recovered from the English-language biomedical literature by use of "carcinogens" or "PhIP" or "B[a]P" or "NNK/NNN" and "plant-based functional foods" or "phytochemicals" or "fruit" or "vegetables" or "herbs" as either a keyword or medical subject heading (MeSH) term in searches of the PubMed bibliographic database. We emphasize the most recent scientific papers from the years 2014–2019.

The role of carcinogens in malignant transformation

Characteristic of carcinogens

Generally speaking, chemical carcinogens are defined as agents causing cancer in humans and experimental animals. It was estimated that chemical carcinogens may affect all of the stages of carcinogenesis [16]. Regarding the pathogenic mechanisms of carcinogens, they are divided into two categories [17, 18]. Firstly, non-genotoxically acting agents, which constitute 10–20% of all carcinogens [19], induce cancer through mechanisms other than genotoxic (such as changes in apoptotic signaling, cell proliferation, intercellular communication, endocrine system, stimulation of oxidative damage or epigenetic alterations [17, 18]) with these processes usually interfering more pathways simultaneously [20]. Despite that some epigenetic agents are also genotoxic, not all non-genotoxic carcinogens function via epigenetic mechanisms [21]. Interestingly, epigenetic changes may occur independently or concomitantly with genotoxic aberrations as they may be a consequence of the exposure to environmental chemicals [21]. On the contrary, genotoxic carcinogens cause DNA damage either directly or after metabolic activation [17, 20] due to their electrophilic activity. Electrophiles are electron-seeking molecules [22] which form adducts with intracellular nucleophilic macromolecules [22, 23]. In case that repairing mechanisms prior to the replication fail to fix the damage, the formation of DNA adducts consequently leads to the carcinogenesis [18]. As exogenous chemicals are associated with the production of reactive electrophilic species (RES), there is an association between RES and DNA adducts, mutations and cancer [22, 23]. Actually, most of known carcinogens are considered to be genotoxic [19] and unlike non-genotoxic carcinogens there is no safe dose or exposure threshold associated with them [17]. Importantly, direct-acting or activation-independent carcinogens interact directly with DNA or cellular components due to electrophilic groups [10], while activation-dependent or indirect-acting carcinogens require activation

to electrophilic forms so that they become carcinogenic or reactive intermediates exerting genotoxic effects [10, 24]. After all, the harmful properties of carcinogenic agents are mediated via exogenously or metabolically generated electrophiles and reactive oxygen species (ROS) [25].

Carcinogen-mediated oxidative damage

A free radical is defined as independently existing molecular species that contains an unpaired electron. Significantly, many radicals are unstable and highly reactive [26]. The balance of various oxidants maintains the cellular homeostasis and protects cells against oxidative stress [23]. ROS generated in excessive quantity contribute to the damage of cell structures [27] due to their ability to oxidize lipids, which are essential components of cell membranes, as well as protein products (enzymes, receptors or membrane transporters). Moreover, the reaction with DNA leads to the formation of DNA adducts and also contributes to the indirect DNA attacking [26, 28]. Interestingly, DNA is considered to be the main target of oxidative damage especially in aging and cancer. Actually, the formation of free radicals and other ROS is mediated via metabolic processes or external sources including air pollutants, cigarette smoke, radiation [26] as well as heavy metals [29, 30], industrial solvents, certain drugs, pesticides [29] or other chemicals [26]. Therefore, free radicals are products of enzymatic reactions such as respiratory chain, prostaglandin synthesis, phagocytosis or cytochrome P450 system or non-enzymatic reactions of oxygen with organic compound or ionizing reactions [26]. Due to the environmental stressors and xenobiotics contributing to the increase of ROS production [23, 31], even a low-dose exposure of carcinogens in human–environment, especially in the conditions of failure in DNA repair mechanisms, may be associated with DNA damage and cancer [23]. Imbalance between ROS and antioxidant defense system is implied in all stages of carcinogenesis [26] because cancer cells are associated with an increase in ROS production due to the aberrant metabolism, energy demand [12], cellular signaling, peroxisomal activity, activation of oncogenes, mitochondrial dysfunction or others [32]. ROS are also involved in the therapy resistance, increase in blood supply of tumors and metastasis. Moreover, ROS may alter genes related to apoptosis, proliferation and transcription factors [12]. Nevertheless, enzymatic antioxidants such as superoxide dismutase (SOD), catalase or glutathione system enzymes (glutathione reductase, glutathione peroxidase, glutathione S-transferase) as well as non-enzymatic antioxidants (vitamin E, vitamin C, glutathione, numerous dietary phytochemicals) protect biomolecules either directly or indirectly against oxidative damage [26]. Figure 1 based on [26, 27, 33] shows mechanisms of free radical formation and toxicity together with the defense mechanism of enzymatic and non-enzymatic antioxidants.

Metabolic activation of carcinogens and their role in the initiation and promotion of carcinogenesis

As stated before, most of the environmental carcinogens exist in the form of procarcinogens and thus require a metabolization. However, metabolic processes may lead to the inactivation, detoxification and an increase in aqueous solubility of these compounds and result in their detoxification and excretion out of the body. On the contrary, activation of carcinogens through a variety of metabolic processes leads to the generation of electrophilic reactive intermediates with an ability to bind to DNA, form DNA adducts and thus contribute to the formation of mutations [10, 24, 34] and initiation of carcinogenic response [8]. Table 1 shows the sources of selected carcinogens that are widely spread in human–environment.

The bioactivation of carcinogens into reactive electrophiles which are capable of covalent binding to DNA [35] is mediated primarily through xenobiotic-metabolizing enzymes mainly cytochrome P450s, also known as CYPs. However, other enzyme systems are also involved in the activation of various carcinogens [10, 24, 34]. Actually, CYPs are defined as enzymes functioning as major oxidative catalysts metabolizing xenobiotic and endogenous compounds and activating carcinogens independently or in conjugation with phase II enzymes [10, 34], while major human CYP enzymes involved in the activation of chemical carcinogens are 1A1, 1A2, 1B1, 2A6, 2A13, 2E1 and 3A4 [36]. Subsequently, reactive metabolites bind to DNA and generate DNA adducts which, if not repaired, lead to damage and mutation in genes and cancer as a consequence [37]. Eventually, environmental carcinogens including PAHs, HAAs or tobacco-related nitrosamines need to be activated through xenobiotic-metabolizing enzymes to become reactive and initiate cell transformation [36]. Table 2 shows a detailed overview of mechanisms of metabolic activation of selected carcinogens.

HAAs and PAHs are associated with an ability to initiate cancer in various tissue types. Their carcinogenicity is related to interactions with the aryl hydrocarbon receptor (AhR) which is defined as ligand-activated transcription factor. AhR protein binds to exogenous ligands causing nuclear translocation of AhR and dimerization with the AhR nuclear translocator protein. The consequent interaction of the heterodimer with consensus DNA sequence xenobiotic responsive element on the enhancer regions of target genes (such as CYP1 family) increases their transcription [9]. Interestingly, most HAAs are considered to be mutagenic [9] and carcinogenic [38]. Therefore, HAAs contribute to the etiology of human malignancies related to dietary intake as

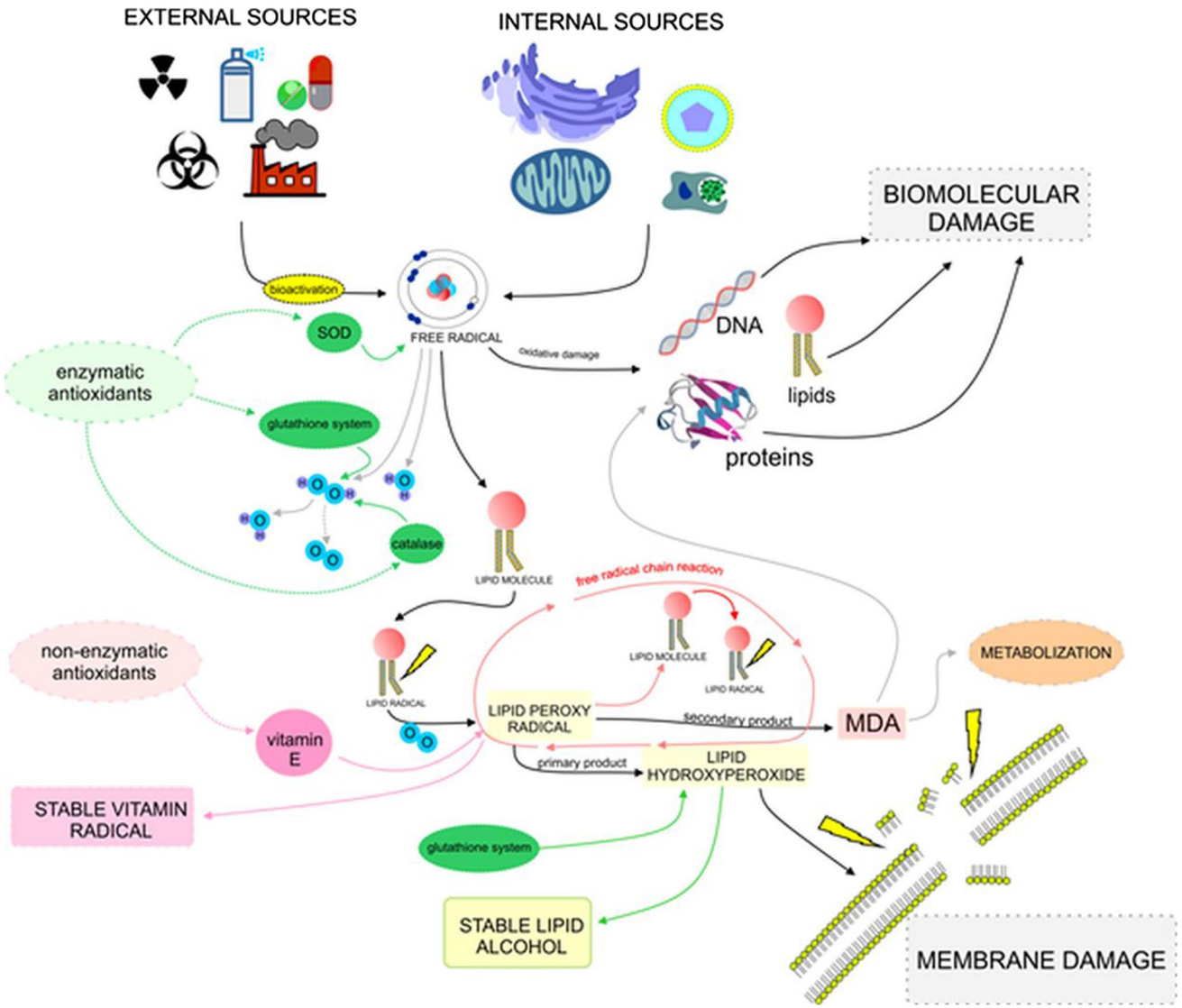

Fig. 1 The formation of free radicals, effects on biomolecules and antioxidant defense system

Table 1 Sources of exposure to PAHs, HAAs and nitrosamines

Carcinogen	Source of exposure	References
PAHs	Cooking processing of meat (roasting, barbecuing, grilling, smoking, baking, etc.)	[124, 125]
	Processed food (nuts, dairy, herbs, beverages, meat products)	
	Tobacco products, automobile exhaust, fossil fuel industry, incomplete combustion of organic materials, forest fires, paper manufacturing, waste incineration	[9, 47, 126]
HAAs	Protein-rich food (meat, meat products, fish) processed at high temperature	[39–41]
	Tobacco smoke condensate and diesel exhaust, incineration ash	
Nitrosamines	Tobacco use	[53, 127]
	Cosmetics, drugs, rubber industry and tobacco	

PAHs polycyclic aromatic hydrocarbons, *HAAs* heterocyclic aromatic amines

Table 2 Mechanisms of metabolic activation of selected carcinogens

Carcinogen		Mechanism of metabolic activation	References
HAAs	PhIP	Initial oxidation (CYP1A2, CYP1A1 and CYP1B1) → **N-hydroxy-PhIP** → further metabolism (by NATs or SULTs) → **N-acetoxy-PhIP, N-sulfoxy-PhIP** → binding to DNA → DNA adducts: **PhIP-C8-dG**	[35, 43, 128]
PAHs	B[a]P	Initial oxidation (CYP1A1, CYP1B1) → **B[a]P 7,8-epoxide** → conversion by epoxide hydrolase → **B[a]P-7,8-dihydrodiol** → activation (CYP1A1 and CYP1B1) → **BPDE** → BPDE + DNA → adducts: **dG-N2-BPDE**	[43]
Nitrosamines	NNK NNN	CYPs → unstable **α-hydroxynitrosamines** → decomposition to **diazohydroxides** → reaction with DNA → **methyl-DNA** adducts, **PHB-DNA** adducts, **POB-DNA** adducts, other **NNN-DNA** adducts	[51]

Explanatory notes: → followed by

B[a]P benzo[a]pyrene, *BPDE* B[a]P-7,8-dihydrodiol-9,10-epoxide, *dG-N2-BPDE* 10-(deoxyguanosin-N2-yl)-7,8,9-trihydroxy-7,8,9,10-tetrahydro-BaP, *HAAs* heterocyclic aromatic amines, *NATs* N-acetyltransferases, *NNK* nitrosoamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, *NNN* N'-nitrosonornicotine, *PAHs* polycyclic aromatic hydrocarbons, *PHB-DNA* adducts, pyridylhydroxybutyl-DNA adducts, *PhIP* 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, *PhIPC8dG* N(deoxyguanosin8yl)2amino1methyl6phenylimidazo[4,5b]pyridine, *POB-DNA* adducts, pyridyloxobutyl-DNA adducts, *SULTs* sulfotransferases

they are present in processed protein-rich food such as meat [7] especially when it is cooked at a high temperature [39, 40]. Despite the cooking temperature, the level of HAAs depends also on the meat product and cooking time with their formation usually mediated via non-enzymatic reaction [7] between sugars, amino acids and creatine occurring at temperature above 150 °C [41]. Actually, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), which is classified as possibly carcinogenic to humans by International Agency for Research on Cancer (IARC) [35, 41], is considered to be one of the most abundant HAAs formed in meat prepared at high temperature [42] and is also found in tobacco smoke [43].

In addition, benzo(a)pyrene (B[a]P) is an Ahr ligand [44] defined as a member of PAHs which is biologically transformed into a potent carcinogen B[a]PDE contributing to the formation of DNA adducts and mutations [45, 46]. IARC classified B[a]P as a human carcinogen [44]. Among a great amount of chemical constituents associated with cigarette smoke, B[a]P is considered to be one of the most potent carcinogenic agent [47] with its exposure related to human malignancies including lung, bladder, skin, oral and esophageal cancer [48]. Interestingly, considering epigenetic modulation of B[a]P, it was associated with alterations in genome-wide H3K9 histone acetylation profile [49], non-coding RNAs and also with changes in global methylation in vitro [48] as well as in a longitudinal cohort study [50].

Moreover, metabolically activated tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), which are classified by IARC as carcinogenic to humans [51], also contribute to the formation DNA adducts and malignancy. Moreover, their binding to the nicotinic acetylcholine receptor promotes cancer growth via enhancement of proliferation, survival, migration and invasion [51–53]. NNAL is the metabolite of NNK considered to be a strong carcinogen found in the urine of both smokers and non-smokers exposed to second-hand smoke [51]. Despite an important role of carcinogens in cancer initiation, they are highly implied in the cancer promotion and progression. Low-dose environmental mixtures and carcinogens are associated with an increase in invasiveness and metastasis mediated via various mechanisms [45]. Table 3 shows selected mechanism of the initiation, promotion, or promotion of cancer by selected HAAs, PAHs or nitrosamines.

The role of phytochemicals in carcinogen exposure

Phytochemicals are defined as non-nutrient plant secondary metabolites [54] present in fruit, vegetable or grains [55] able to reduce the risk of various diseases [56]. Terpenoids, alkaloids, isothiocyanates and polyphenols are considered to be the most studied phytochemicals associated with oxidative damage [54]. Actually, as shown in Fig. 2, phytochemicals function via various overlapping and complementary mechanisms including antioxidant (A) and detoxifying abilities (B), binding/dilution of carcinogens in digestive tract (C), epigenetic alterations (D) or modulation of cellular and signaling pathways (E) [57].

Particularly, phytochemicals exert great antioxidant and free radical scavenging activity [58], prevent DNA damage and consequently inhibit cancer initiation [12]. The protective role of phytochemicals against carcinogen-induced oxidative stress is evaluated using 8-oxo-deoxyguanosine (8-oxo-dG) or nitrotyrosine as markers of oxidative DNA damage and nitrosative stress [59, 60]. Phytochemicals also promote detoxification and enhanced excretion of exogenous or endogenous carcinogens [11, 61] through inhibition of Phase I enzymes bioactivating carcinogens or induction of Phase II enzymes [62–65] such as glutathione S-transferase (GST) or UDP-glucuronosyltransferase (UGT) [66] metabolizing carcinogens to

Table 3 Impact of PhIP, B[a]P, NNK and NNN on carcinogenesis initiation or promotion

Carcinogen	Model	Mechanisms	Effect	References
PhIP	Male Fischer 344 rats	Human prostate tissue metabolically activating N-hydroxy-PhIP occurring after its N-hydroxylation in the liver	→ genotoxic species and DNA adducts	[42]
PhIP + E2	Human breast adenocarcinoma cell line (MCF-7)	Alterations in microRNA expression	↑ tissue-specific carcinogenicity and estrogenic activity of PhIP → initiation and progression of breast cancer	[128]
PhIP + ethanol	ER-α positive human mammary cell line	–	↑ oxidative stress and genotoxicity	[89]
PhIP + DSS	CYP1A-humanized mice	Possible role of Lgr5 + stem cells; *Ctnnb1/β-catenin* mutation in residual epithelial cells	→ carcinogenesis initiation	[129]
PhIP	Breast cancer cell lines MCF-7 and T47D	Modulation of cathepsin D, COX-2 and MMP activity	↑ invasiveness	[130]
B[a]P	Murine model	G to T transversions in the mutation hot spots region of p53 gene	→ murine papillomas and squamous cell carcinomas	[131]
	Gastric cancer cell lines (SGC-7901 and MNK-45)	AhR receptor and ERK-dependent induction of MMP9 and c-myc	↑ proliferation, migration and invasion	[132]
	Breast cancer model in vitro and in vivo	Upregulation of ROS-induced ERK signaling leading to activation of MMP9	↑ migration	[133]
	Lung adenocarcinoma H157 cells	Upregulation of TGIF	↑ migration, invasiveness and metastasis	[134]
LMW PAHs + B[a]P	Mouse non-tumorigenic type II cell line (C10)	↑ BPDE-DNA adducts, inhibition of GJIC and induction of COX-2	↑ carcinogenic potential	[135]
NNK	Lung cancer	Modulation of cSrc/PKC/focal adhesion kinase loop	↑ invasiveness and migration	[45]
NNK and NNN	–	Deleterious mutations in oncogenes and tumor suppression genes by forming DNA adducts	→ tumor initiation	[53]
NNK and NNN binding to nicotinic acetylcholine receptor	–	Enhancing and deregulating cell proliferation, survival, migration and invasion, thereby adjustment of microenvironment for tumor growth	↑ tumor growth	[53]

Explanatory notes: ↑ increase, promotion; → induction, formation; + and, in combination with

AhR aryl hydrocarbon receptor, *B[a]P* benzo[a]pyrene, *BPDE* benzo[a]pyrene-7, 8-dihydrodiol-9, 10-oxide, *COX-2* cyclooxygenase-2, *DNA* deoxyribonucleic acid, *DSS* dextran sodium sulfate, *E2* 17-*β*-estradiol, *ERK* extracellular signal-regulated kinase, *ER-α* estrogen receptor alpha, *GJIC* gap junctional intercellular communication, Lgr5 + leucine-rich repeat-containing G protein-coupled receptor 5, *LMW PAHs* low molecular weight polycyclic aromatic hydrocarbons, *MMP* matrix metalloproteinase, *NNK* nitrosoamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, *NNN* N'-nitrosonornicotine, *PhIP* 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, *PKC* protein kinase C, *ROS* reactive oxygen species, *TGIF* TG-interacting factor

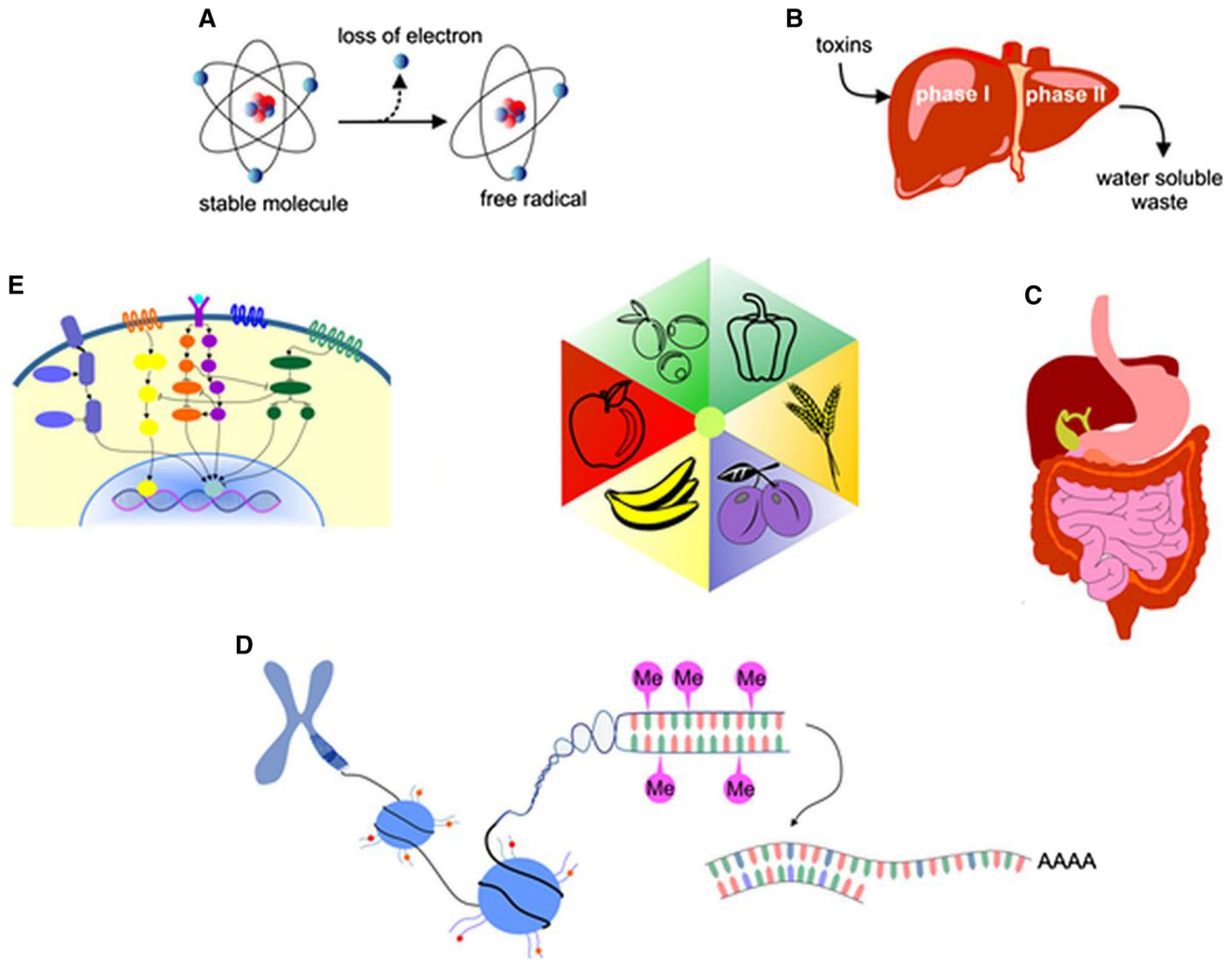

Fig. 2 Targets of phytochemicals efficacy against carcinogen-associated malignant transformation

more excretable forms [62–65]. Significantly, chronic pro-inflammatory signaling caused by continuous imbalance of redox homeostasis may lead to induction of pro-oncogenes or anti-apoptotic factors [67]. Above all, phytochemicals are potent modulators of inflammatory pathways which are activated by various sources including carcinogens through regulation of signaling molecules, e.g., nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT-3) [68] and the expression of COX-2 which catalyzes the formation of pro-inflammatory prostaglandins [60]. The imbalance in these pathways contributes to the tumor cells survival, proliferation or invasion [68]. Additionally, phytochemicals prevent deregulation of other cancer-critical signaling elements or pathways (such as PTEN/PI3K/Akt [60], Ki-67 [60] or MAPK [46]) and thus inhibit the proliferation and induce apoptosis of cancer cells in various stages of carcinogenesis [11, 12]. Moreover, exposure to internal processes as well as external sources including environmental chemicals, pollution, tobacco, alcohol or endocrine disruptors may affect epigenome [69] and cause aberrations in histone modifications, DNA methylation and miRNA expression leading to the modification of expression of various oncogenes or tumor-suppressor genes [70]. Interestingly, environmental exposure-related epigenetic impairment may cause damage in fetus thus influencing disease risk later in life [13]. Nevertheless, phytochemicals target and reverse epigenetic changes occurring during carcinogenesis [71]. Moreover, bioactive food compounds modulating epigenetic markers reduce inflammatory responses via suppression of NF-κB activation [72]. Therefore, bioactive foods may initiate protective epigenetic modifications throughout the whole life with the nutrition of developing organism to be particularly important [13]. Accordingly, Fig. 3 shows an overview of mainly experimental studies focusing on phytochemicals exerting an ability to modulate the formation

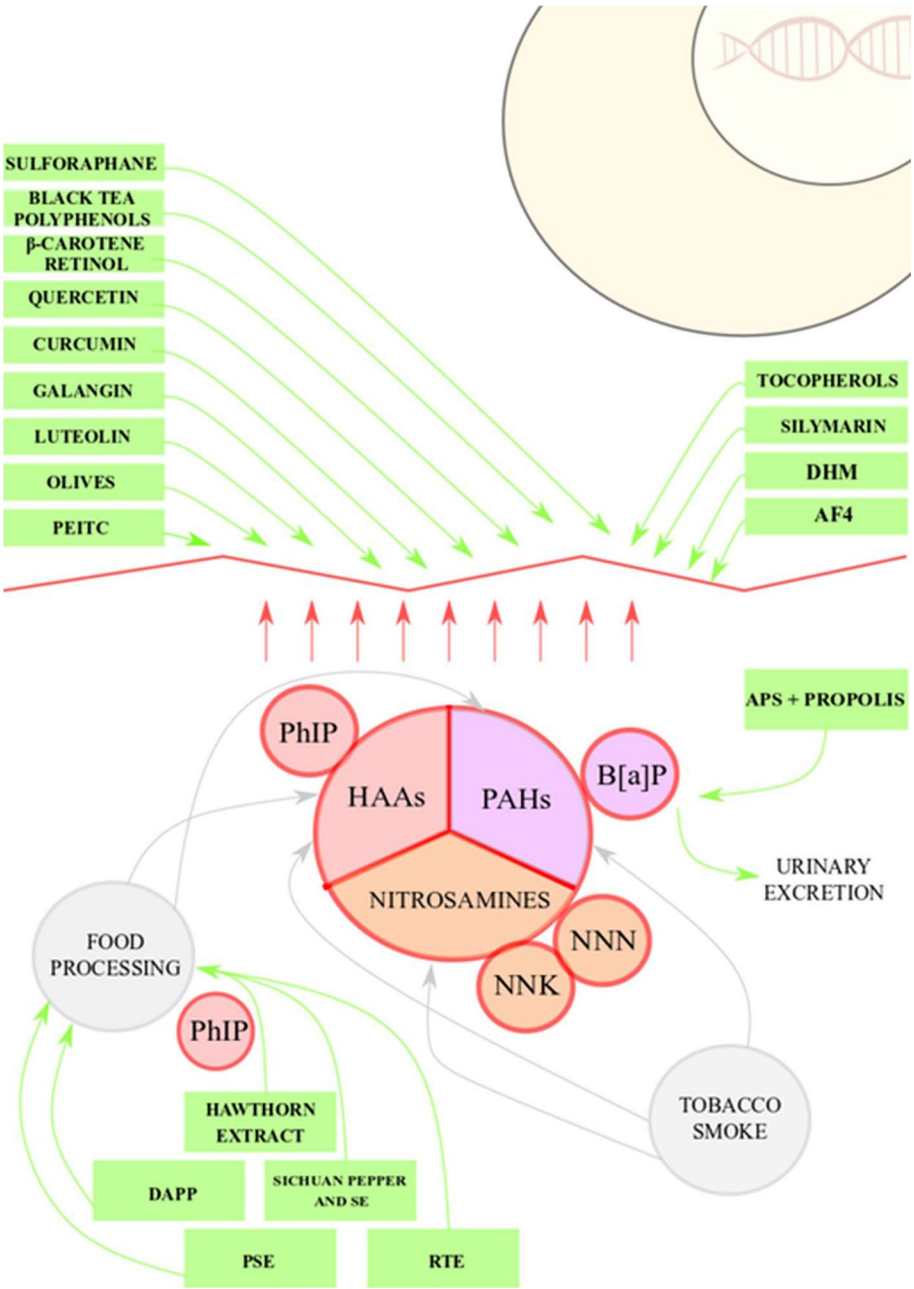

Fig. 3 Effects of dietary phytochemicals (isolated or mixtures) on carcinogen exposure or formation. APS, aloe polysaccharide; B[a]P, benzo[a]pyrene; DAPP, polyphenol-rich dried apple peel extract; DHM, dihydromethysticin; HAAs, heterocyclic aromatic amines; NNK, nitrosoamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine; PEITC, phenethyl isothiocyanate; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; PSE, pomegranate seed extract; RTE, Rosa rugosa tea extract; SE, sanshoamide extract

of carcinogens or protect cells against carcinogen exposure [41, 46, 58–60, 66, 73–88].

PhIP

Protein-rich food cooked at high temperature and the use of tobacco products are well-known sources of HAAs [39–41]. PhIP, as one of the most abundant HAAs, is associated with inducement of several types of malignancy including breast, colon or prostate cancer [42, 45] and is considered to be DNA damaging, mutagenic and estrogenic agent with the toxicity involving CYPs-mediated metabolic activation, transcriptional responses through AhR and estrogen receptor-alpha (ER-α) [89]. As HAAs are potent carcinogens formed during cooking processes of meat and meat products [41], we provide several studies evaluating an impact of natural compounds on the formation of HAAs during food processing. Interestingly, Szterk [90] demonstrated that HAAs generated in grilled beef are produced in a free form and as chemically or physicochemically bonded compounds. The evaluation of these samples digested in in vitro model segments of human digestive tract revealed an increase in the level of free HAAs due to the proteolytic enzymes [90]. Nevertheless, the protective role of natural antioxidants

against the formation of HAAs in cooking processes was analyzed in several studies. *Rosa rugosa* tea extract (RTE) is known source of phenolic compounds and is also associated with an ability to inhibit formation of free radicals. Actually, RTE inhibited formation of HAAs in meat patties at different temperature. Interestingly, an amount of total HAAs in ground beef patties fried at 160 °C decreased by 75% and by 46% at 220 °C. Considering individual HAAs, RTE is highly effective especially against the formation of PhIP at 220 °C ($p < 0.001$) and at 160 °C ($p < 0.05$) [41]. Similarly, it was demonstrated that hawthorn extract at 0.5% and 1% could reduce HAAs formation in beef and chicken meat cooked at high temperature [75]. Sichuan pepper widely used in cooking and also as herbal medicine in Asian cultures and sanshoamide extract also inhibited formation of HAAs in grilled ground beef patties. Apart from effects of other HAAs evaluated in this study, the rate of PhIP was significantly inhibited by 82% when treated with a low-concentration pepper (0.5%) and by 27% when treated with a low-concentration sanshoamide extract (0.005%) [91]. Actually, pomegranate seed extract inhibited PhIP formation by 68% in beef meatballs and by 75% in the chicken meatballs with these result dependent on the cooking methods [73]. Polyphenol-rich dried apple peel extract (DAPP) inhibited the formation of HAAs including PhIP in pan fried beef patties suggesting the useful way to minimize the generation of these genotoxic products during preparing beef [74]. Paradoxically, results of the epidemiological studies are not so clear as compared to a clinic-based case control study in which no association between consumption of well-done meat, as a source of meat mutagens, and pancreatic cancer was found [92]. Similarly, prospective analysis revealed that meat mutagens were not significantly associated with risk of colorectal cancer. However, results concerning the PhIP from red meat needed further investigation [93]. On the contrary, the case–control study demonstrated that the exposure to PhIP and 2-amino-3,8-dimethylimidazo-(4,5-f) quinoxaline (MeIQx) mediated via intake of processed meat may increase the risk of renal cell carcinoma [94]. Apart from the effects of phytochemicals on the food processing, the effects of natural substances on PhIP-induced damage were demonstrated also in preclinical research. Actually, curcumin inhibited the formation of PhIP-induced DNA adducts and DNA double stand breaks and decreased the production of ROS in normal breast epithelial cells (MCF-10A) [87]. Another study evaluated whether various forms of tocopherols other than α-T, as the major forms of vitamin E, possess higher preventive efficacy in a model of prostate carcinogenesis induced by PhIP in the CYP1A-humanized mice. Eventually, administration of γ-T-rich mixture of tocopherols (γ-TmT) inhibited mouse prostatic intraepithelial neoplasia via reduction of cellular oxidative and nitrosative stress thus prevented changes leading to enhanced proliferation or inflammation. Moreover, γ-TmT also reduced PhIP-induced aberrations in p-AKT and PTEN, signaling pathways often deregulated in prostate cancer. According to further analysis, purified δ-T was more effective preventive agent against mouse prostatic intraepithelial neoplasia and p-AKT elevation when compared with purified α-T or γ-T [60]. Similarly, δ- and γ-tocopherols reduced colon tumor formation, suppression of oxidative and nitrosative markers and pro-inflammatory mediators and consequent protection against early cellular and DNA damage in PhIP-induced colon carcinogenesis promoted by dextran sodium sulfate-induced colitis in CYPA1-humanized mice [59]. Interestingly, sulforaphane and quercetin reduced the level of PhIP-DNA adducts in a dose-dependent manner and thus increased the rate of detoxification of the PhIP in intact human HepG2 cells. However, the above-mentioned dietary isothiocyanates and flavonoids did not show any effect on the rate of PhIP-DNA adduct repair [66]. Last but not least, Fucceli et al. [76] evaluated preventive efficacy of phenolic extracts from olive, olive oil and olive leaves on genotoxicity caused by heterocyclic amines including PhIP in freshly isolated human peripheral blood mononuclear cells. Interestingly, DNA damage preventive effects were associated with all of the phenolic extracts in very low concentrations which can be reached in human tissue via regular intake of olive oil [76].

B[a]P

Environmental factors, mostly tobacco smoke containing more than 60 different carcinogens, are strongly associated with lung cancer [37]. PAHs and nicotine together with NNK are components of tobacco smoke causing alteration of cancer-related genes, DNA repair or apoptosis-related genes [95]. Therefore, B[a]P exerts a crucial role in the lung carcinogenesis. Importantly, the model of B[a]P-induced lung cancer in mice is widely used to evaluate the efficacy of natural products in this approach [96]. Anti-initiating efficacy of sulforaphane against B[a]P-induced lung carcinogenesis was evaluated in mouse model in vivo. Importantly, sulforaphane decreased carcinogen-induced stress via inhibition of B[a]P-induced AhR activation resulting in the decrease of phase I enzymes, enhancement of nuclear factor erythroid 2-related factor 2 (Nrf2) transcription and induction of phase II enzymes [77]. Moreover, curcumin was demonstrated to reverse B[a]P ingestion-associated histopathological deviations in the lung tissues and to reduce B[a]P-induced activation of NF-κB and MAPK signaling and COX-2 transcription in Swiss albino mice [46]. Antioxidant and antitumor efficacy of dietary flavone luteolin was evaluated in B[a]P-induced lung carcinogenesis in Swiss albino mice. Actually, oral administration of B[a]P increased lung specific tumor markers and decreased levels of enzymatic and non-enzymatic antioxidants. The administration

with luteolin (15 mg/kg body weight, p.o) counteracted all these changes and maintained cellular normalcy. Interestingly, luteolin treatment was also associated with negation of B[a]P-induced expression of nuclear NF-κB, proliferating cell nuclear antigen (PCNA) and cytochrome P450 1A1 (CYP1A1) thus confirming its chemopreventive potential in B[a]P-induced lung experimental carcinogenesis [78]. Interestingly, *β*-carotene and retinol reduce B[a]P-induced mutagenicity and oxidative stress via modulation of xenobiotic-metabolizing enzymes in HepG2 cell line. Therefore, it is highly recommended to include food rich in these compounds into the diet in the areas of high PAHs pollution [79]. The effectiveness of galangin, a dietary flavonol, in the inhibition of tumor initiation was evaluated in experimental pulmonary tumorigenesis induced by B[a]P in male Swiss albino mice. Actually, an increase in activity of phase I drug metabolic enzymes, LPO levels, tissue marker enzymes and decreased activity of phase II metabolic enzymes as well as antioxidant levels were observed in B[a]P-induced animals. Nevertheless, administration of galangin (20 mg/kg body weight) counteracted all mentioned anomalies and restored cellular homeostasis [80]. Polymeric black tea polyphenols were found to modulate B[a]P and NNK-induced lung carcinogenesis in A/J mice. Dose-dependent anti-initiating effects were mediated via induction of phase II and inhibition of carcinogen-induced phase I enzymes which led to the decrease in BPDE-DNA adducts. Moreover, the inhibition of cancer promotion due to black tea polyphenols was demonstrated via decrease in cell proliferation and increase in apoptosis [97]. Moreover, dietary intake of isothiocynates is strongly associated with cancer chemopreventive efficacy. 2-Phenethyl isothiocyanate (PEITC) which is found in watercress and cruciferous vegetable [81] was demonstrated to modulate biotransformation of enzymes required for metabolism of carcinogens. The determination of CYP1A1 mRNA and apoprotein levels in B[a]P-treated rat liver slices revealed an ability of PEITC to inhibit bioactivation of the mentioned carcinogen [82]. Similarly, silymarin modulates phase I detoxification enzyme CYP1A1 and phase II conjugating enzymes thus preventing B[a]P-induced toxicity in Wistar rats [83]. On the contrary, fruit and vegetable are also a source of PAHs as they may be transferred from air and soil or during the process of cultivation. Moreover, the presence of PAHs in fruit and vegetable may be related to transport and/or storage or cooking processes. Usually, there is a small amount of PAHs in fruit and vegetable; however, products grown near roadways or in urban regions are associated with an increase in the level of PAHs [98]. Significantly, the detoxification effects of aloe polysaccharide (APS) and propolis on the urinary excretion of tobacco carcinogens B[a]P and cotinine, a nicotine metabolite, were investigated in smokers. In comparison with the control group, there was an increase in the level of urinary expression of B[a]P and cotinine in a time-dependent manner after supplementation with the mixture of APS and propolis (B[a]P, 2.33-fold; cotinine, 2.28-fold), APS (B[a]P, 2.23-fold; cotinine, 2.64-fold) and propolis (B[a]P, 1.30-fold; cotinine, 2.08-fold). The above-mentioned results suggest that APS and propolis or its mixture increase B[a]P and nicotine urinary excretion thus reduce the risk of cancer or other diseases [84]. Despite the exposure B[a]P through tobacco smoke, over-cooked meat or other sources, the inhibition of enzymes required for its bioactivation may represent an efficient chemopreventive strategy against carcinogen-mediated health effects [82].

NNK and NNN

Due to the metabolic activation in target tissues, nitrosamine NNK and its metabolite NNAL are associated with organ-specific carcinogenicity [51] and therefore contributing to the lung, pancreas and other cancer types [52]. Importantly, the absorption of NNK is mediated primarily via direct inhalation of the mainstream smoke by smokers. Non-smokers exposition to NNK is the result of the inhalation of second-hand smoke from exhaled mainstream smoke or sidestream smoke. Moreover, users of smokeless tobacco products absorb NNK orally. Additionally, NNK may be absorbed orally through ingestion of NNK-containing dust and also dermally via NNK-contaminated surfaces [99]. Importantly, the study evaluating urinary levels of tobacco-specific nitrosamines showed that children exposed to environmental tobacco smoke (ETS) had two times higher level of total urinary and free NNAL as well as lower ability to detoxify NNAL when compared with passive smoking adults. According to that, third-hand smoke may be considered to be a source of environmental tobacco exposure increasing the risk of ETC-induced health consequences in children [100]. As was demonstrated by Khariwala et al. [101] smokers with oral/head and neck squamous cell cancer (HNSCC) showed higher levels of tobacco-specific nitrosamines-derived oral DNA damage in comparison with cancer-free smokers with similar level of carcinogen and nicotine exposure in both groups. These results suggested dissimilarities in the formation of adducts or DNA repair of individuals included in the study. Therefore, the formation of DNA adducts independent from indicators of carcinogen exposure may be a predictor of HNSCC development in smokers [101]. Nevertheless, khaini is defined as a smokeless tobacco extract (STE) with a NNK as its one of the carcinogenic components. Actually, STE led to the increase in expression and activation of NF-κB and its target COX-2 in in vitro oral cell system of human. Significantly, curcumin pretreatment of oral premalignant and cancer cells in vitro suppressed nuclear translocation and DNA-binding activity of NF-κB induced by STE [85]. The protective efficacy of apple peel flavonoid fraction (AF4) rich in flavonoids and phenolic

acids such as quercetin glycosides, epicatechin, cyanidin 3-galactoside, chlorogenic acid and phloridzin against DNA damage induced by various carcinogenic chemical agents was evaluated in normal human bronchial cells in the lung (BEAS-2B). The DNA damage was induced by nicotine-derived nitrosoamine ketones NNK, NNK acetate, methotrexate and cisplatin due to the ability of these carcinogens to reduce the viability of normal cells via enhancement of the ROS levels and modulation of cell death mechanisms. Eventually, pretreatment of AF4 protected BEAS-2B cells against carcinogens, especially nicotine-derived nitrosoamine ketones and thus against oxidative DNA damage and facilitate DNA repair mechanisms [58]. Considering inhibitory efficacy of PEITC against metabolic activation and lung carcinogenicity of the NNK in rodent models, Yuan et al. [81] conducted a clinical trial to determine inhibitory activity of PEITC in smokers. Eventually, PEITC treatment led to the reduction of NNK metabolic activation by 7.7%. Nevertheless, modest, specific and significant result of this clinical trial provides a promising potential of PEITC as an inhibitor of carcinogen metabolism in smokers [81]. Moreover, PEITC inhibits P450-mediated bioactivation of NNK and also induced detoxification enzymes [102]. A natural product from *Piper methysticum* dihydromethysticin (DHM) is considered to be a promising preventive agent of lung carcinogenesis as it dose-dependent blocked NNK-induced O6-Methylguanine in C57BL/6 female mice. As there were no differences in mice from Ahr ± and Ahr −/− backgrounds, the mechanism is independent of the AhR pathway [86]. Table 4 shows an overview of preclinical and several clinical studies evaluating the effects of some plant functional foods or isolated phytochemicals on selected carcinogen-induced malignancies.

Conclusion and future directions

Due to the presence of potential harmful chemicals in the environment concerning either our diet or other lifestyle factors discussed in this review, we emphasize an important role of compounds present in food rich in fruit and vegetable against exposure to carcinogens. Importantly, levels of enzymes metabolically activating and detoxifying chemicals are influenced by both genetic and environmental factors [8]. Despite the inconclusive results of epidemiological studies concerning an association between HAAs and the risk of malignant disease, the results of preclinical (and a few of the listed clinical studies) point out a significant effect of plant nutrients on the inhibition of harmful effects of carcinogens widely spread in the human–environment. Various phytochemicals reduced the carcinogenic effects of HAA-induced carcinogenesis as well as minimize the formation of carcinogens during the processing of food. Tobacco smoke is associated with the presence of PAHs and nitrosamines that contribute to the development of lung cancer and other types of malignancies. The protective efficacy against exposure to these compounds was also demonstrated in the mentioned studies. Considering the harmful effects of carcinogens on the health of adults and especially developing organisms, the inclusion of phytochemicals in human diet should be taken into consideration.

Chemoprevention by dietary phytochemicals, mediated by significant geno-protective effects, is an acceptable clinical approach in the managing of carcinogenesis because of the simply application and cost-effectiveness. The multimodal clinical using of phytochemicals as multifunctional compounds in oncology is very promising because these compounds are capable of reversing or stopping neoplastic transformation of premalignant cells on genomic level, with the aim to preserve healthy cells or prevent the gaining of their tumor phenotype [103]. It is proposed that phytochemicals (mainly as natural mixtures present in whole plant foods) associated with efficacious antioxidant activities toward the cell genomic macromolecules may play potentially crucial role as primary chemopreventive agents in the initiation phase of carcinogenesis [104]. Free radical scavenging activity, increased expression of endogenous antioxidant enzymes, increased DNA repair mode of action, affecting the metabolic activation/inactivation of carcinogens, detoxification and suppression of pro-oxidant enzymes in the cell are consequential oncostatic mechanisms of action well documented in phytochemicals [105–108]. The above-mentioned mechanisms favor dietary phytochemicals as molecules able to inhibit the initiation phase of carcinogenesis and therefore are useful in primary chemoprevention. However, since phytochemicals are capable of interfering with the molecular mechanisms of tumor growth and metastatic spreading, the concept of chemoprevention has been broaden to affect all three stages of carcinogenesis: apart from prevention of cancer initiation through the above-mentioned mechanisms, it includes also prevention of tumor promotion (tumor onset) and progression through inhibition of proliferation, angiogenesis and cancer stem cells, induction of apoptosis and differentiation, modulation of immunity and epigenetic mechanisms of action and decreasing of pro-inflammatory regulation [15, 56, 109–115]. With more detailed evaluation of the potential molecular targets of phytochemicals in different tissues/organs and tumor clones and types with different genotypes/phenotypes, the mechanistic preclinical data coupled with clinical studies could provide the final and anticipated clinical recommendations of these natural substances in primary, secondary and tertiary chemoprevention of cancer disease [116].

Since the crucial aim of primary chemoprevention is the reduction of cancer incidence in the general population and those at high risk of developing the disease,

Table 4 Effects of dietary phytochemicals (isolated or mixtures) on carcinogen exposure or formation

Dietary compound	Study details	Effect/mechanism	References
RTE	–	Inhibited formation of total HAAs and individual HAAs, especially PhIP in beef patties fried at 160 °C and 220 °C	[41]
Hawthorn extract	–	↓ HAAs formation in beef and chicken cooked at high temperature	[75]
Sichuan pepper (Zanthoxylum bungeanum) + sanshoamide extract	–	Inhibited formation HAAs including PhIP in grilled ground beef patties	[91]
DAPP	–	Inhibited formation of HAAs in pan fried beef patties	[74]
PSE	–	Inhibited formation of PhIP in beef and chicken meatballs	[73]
Curcumin	PhIP-induced cytotoxicity in normal breast epithelial cells (MCF-10A)	Inhibition of PhIP-induced DNA adduct formation and DNA double stand breaks ↓ ROS	[87]
Dietary tocopherols (γ-TmT, 0.3% in diet)	PhIP-induced carcinogenesis in CYP1A-humanized mice	↓ oxidative and nitrosative stress Inhibition of prostatic intraepithelial neoplasia ↓ 8-oxo-dG, COX-2, nitrotyrosine, Ki-67 ↑ Nrf2↓ elevation of p-AKT and the loss of PTEN	[60]
Dietary tocopherols (δ-T + γ-T, 0.2% in diet)		↓ colon tumor formation ↓ 8-oxo-dG and nitrotyrosine ↓ NF-κB p65 and p-STAT3	[59]
Sulforaphane (1–10 micro M) and quercetin (5–20 micro M)	PhIP-exposed HepG2 cells	Sulforaphane: ↑ phase II detoxification enzymes, UDP-glucuronosyltransferase 1A1, glutathione S-transferase A1 mRNA expression	[66]
Phenolic extracts from olive, olive oil and olive leaves	PBMC	↓ HAAs-induced genotoxicity	[76]
Sulforaphane	B[a]P-induced lung carcinogenesis in Female Swiss Albino mice	Inhibition of B(a)P-induced AhR activation and induction of Nrf2 mRNA → modulation of phase I and II enzymes (↓ phase I monofunctional oxygenases) ↑ Nrf2 transcription ↑ phase II enzymes	[77]
Curcumin	B[a]P-induced carcinogenesis in Swiss Albino mice ↓ MAPK ↓ COX-2	↓ B(a)P-induced activation of NF-κB	[46]
Luteolin	B[a]P-induced lung carcinogenesis in Swiss Albino mice	↑ levels of enzymatic (SOD, CAT, GR, GPx, GST) and non-enzymatic antioxidants (GSH, vitamin E, vitamin C) ↓ LPO ↓ CEA ↓ NSE ↓ B(a)P-induced expression of NF-κB ↓ PCNA ↓ CYP1A1 ↓ NF-κB	[78]
β-carotene + retinol	B[a]P-induced mutagenicity in HepG2 cell line	↓ ROS ↓ phase I xenobiotic-metabolizing enzymes ↑ phase II and III xenobiotic-metabolizing enzymes	[79]

Table 4 (continued)

Dietary compound	Study details	Effect/mechanism	References
Galangin	B[a]P-induced lung carcinogenesis in Swiss albino mice	↓ phase I drug metabolic enzymes (cytochrome P450, cytochrome b5, NADPH cytochrome P450 reductase and NADH cytochrome b5 reductase) ↓ LPO levels ↓ tissue marker enzymes ↑ phase II metabolic enzymes (glutathione S-transferase, DT-diaphorase and UDP-glucuronyl transferase) ↑ antioxidant levels	[80]
Polymeric black tea polyphenols	B[a]P and NNK-induced lung carcinogenesis in A/J mice	↓ phase I enzymes ↑ phase II enzymes ↓ BPDE-DNA adducts ↓ cell proliferation ↑ apoptosis	[88]
PEITC	Rat liver	↓CYP1A1 mRNA and apoprotein levels	[82]
Silymarin	Wistar rats	↓ CYP1A1 ↑ phase II conjugating enzymes	[83]
*APS + propolis	4 groups of smokers supplemented with 600 mg/day of APS; 600 mg/day of propolis; 600 mg/day of the mixture of APS (420 mg/day) and propolis (180 mg/day) and control group	↑ urinary excretion of B(a)P and nicotine	[84]
Curcumin	Smokeless tobacco exposed oral premalignant and cancer cells	↓ NF-κB ↓ COX-2 ↓ cell viability ↑ apoptosis	[85]
AF4	NNK, NNK acetate, methotrexate and cisplatin exposed BEAS-2B cells	↓ cytotoxicity ↓ total ROS generation ↓ DNA fragmentation ↓ DNA tail moment ↑ repair mechanisms	[58]
DHM (1 mg/g of diet)	C57BL/6 Female Mice	Blockage of NNK-induced O6-Methylguanine	[86]
*PEITC	Smokers ($n = 82$)	↓ NNK metabolic activation	[81]

Explanatory notes: *clinical trial; ↑ increase, promotion; ↓ decrease, reduction; + and, in combination with

8-oxo-dG 8-oxo-deoxyguanosine, *AF4* apple flavonoid fraction, *ALDH1A1* aldehyde dehydrogenase 1A1, *APS* aloe polysaccharide, *AhR* aryl hydrocarbon receptor, *B[a]P* benzo[a]pyrene, *BPDE* benzo[a]pyrene-7, 8-dihydrodiol-9, 10-oxide, *CAT* catalase, *CEA* carcinoembryonic antigen, *COX-2* cyclooxygenase-2, *CYP* cytochrome P450, *DAPP* polyphenol-rich dried apple peel extract, *DHM* dihydromethysticin, *DNA* deoxyribonucleic acid, *GPx* glutathione peroxidase, *GR* glutathione reductase, *GSH* glutathione GST, glutathione S-transferase, *HAAs* heterocyclic aromatic amines, *LPO* lipid peroxide, *MAPK* mitogen-activated protein kinase, *NF-κB p65* nuclear factor kappa B p65 subunit, *NNK* nitrosoamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, *NNN* N'-nitrosonornicotine, *Nrf2* nuclear factor erythroid 2–related factor 2, *NSE* neuron-specific enolase, *p-Akt* phospho-Akt, *PBMC* peripheral blood mononuclear cells, *PCNA* proliferating cell nuclear antigen, *PEITC* phenethyl isothiocyanate, *PhIP* 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, *PSE* pomegranate seed extract, *p-STAT3* phospho-STAT3, *PTEN* phosphatase and tensin homolog, *ROS* reactive oxygen species, *RTE* Rosa rugosa tea extract, *SOD* superoxide dismutase, γ-TmT γ-T-rich mixture of tocopherols

chemopreventive compounds vary in their effectiveness depending on the genotype of the individual exposed to them [117]. Therefore, combination of several phytochemicals or its natural mixtures present in plant foods seems to be better choice to suppress carcinogenesis in oncological practice. Our recent review summarized that numerous preclinical and clinical studies referred to higher efficacy of whole plant (functional) foods against carcinogenesis when compared with single phytochemicals [104]. Based on the critical assessment of the data from recent breast and prostate cancer research, mixture of a wide spectrum of phytochemicals with large amount of biological activities present in plant-derived functional foods could have additive or synergistic effects against cancer which provide an advantage in cancer treatment compared with single phytochemicals [104, 118]. Apparently, the preference of plant-based functional foods over single phytochemicals may present logical and effective approach in the management programs of malignant diseases [104, 119]. On the other hand, there is an apparent lack of results validating these findings in clinical research. From this reason, precisely designed animal studies and clinical trials evaluating the superiority of anticancer activity of one over the other are necessary to establish their potential role in the management of cancer patients.

Contextually, an identification of the transformation-specific genomic signatures and well-defined and confirmed anti-neoplastic activities of isolated phytochemicals (or their natural mixtures) is essential for predictive diagnostics and targeted clinical procedures including cancer chemoprevention [120, 121]. Finally, the advanced medicinal approach based on the predictive, preventive and personalized medicine is considered as the medicine of the future in the overall cancer management [122, 123].

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Human participants and/or animals rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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