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Review Article

Polyphenols: Major regulators of key components of DNA damage response in cancer

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ABSTRACT

DNA fidelity is constantly endangered by various types of intrinsic damages and extrinsic damages. Cells that are affected by DNA damage employ a specific, intricate, and interconnected network of cellular and molecular events (known as DNA damage response (DDR)) in order to maintain genome stability. More importantly, DDR is employed to pass intact genomes on to the next generation. Polyphenols constitute a large group of plant-based secondary metabolites widely present in foods and beverages with plant origins (e.g., fruits, vegetables, grains, spices, soy, essential oils nuts, tea, and wine). Based on chemical structures, polyphenols are grouped into three major phytochemical classes: phenolic acids, flavonoids and non-flavonoids. In this review, we aim to explain how polyphenolic compounds modulate DDR sensors, transducers and mediators, with discussion of how polyphenols modulate apoptosis in response to DNA damage in various types of cancer.

1. Introduction

DNA is constantly subjected to various types of intrinsic damages such as enzymatic conversions in bases, replication errors, and by-products of metabolic activities or extrinsic damages, including ionizing radiations (IR), alkylating agents, benz(o)pyrene, aflatoxins, and electrophilic reactant metabolites. These extensively threaten the integrity and stability of whole genome [1]. To maintain genomic stability and more importantly, to pass intact genomes on to the next generation, a specific, intricate, and interconnected network of cellular and molecular events namely DNA damage response (DDR) comprised of protein kinases-based intra- and inter-cellular signaling pathways, is triggered by affected cells [2]. DDR eliminates the critical and dangerous conditions of the cell through a cascade of three major events: sensing DNA damage, transducing the damage signal into downstream effectors, and finally deciding on the fate of the damaged cell [3]. If the DNA damage is repairable after the cell cycle arresting, the DNA repair machine enters action and guarantees the survival of the cell by eliminating the damage. If the damage is severely irreparable, however, the cellular response enter the cell death or apoptosis phase [4]. Collectively, the bottom line is to prevent a broad range of genomic aberrations, such as point mutations, chromosomal translocations, gain or loss of chromosomal segments or entire chromosomes, all sources of pathological conditions, such as cancer, accelerated ageing, neurodegenerative disorders, as well as immune deficiencies and infertility [5]. Given the significance of DDR to cellular health, targeting it at different levels in order to modulate cellular response is a final goal of various research studies in multiple fields, particularly cancer [6]. In this context, polyphenols are potential and well-studied candidates. ;These phytochemicals are considered one of the most important dietary compounds with antioxidant and chemopreventive properties [7]. An increasing body of research has shown that dietary polyphenolic compounds promote human health [8–12] through tight suppression of the development of degenerative diseases, such as cancer [8,9], cardiovascular diseases [10,11], and metabolic disorders [12]. Therefore, the present review discusses the function of various polyphenolic compounds in regulating DDR by explaining the radical scavenging role of polyphenols in protecting against DNA damage, as well as their modulatory effects of the four major components of DDR; sensors, transducers, mediators, and effectors.

2. Polyphenols

All compounds with at least one aromatic ring and at least one

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hydroxyl functional group, under the rubric polyphenols, constitute a large group of plant secondary metabolites which are widely present in foods and beverages of plant origins (e.g., fruits, vegetables, grains, spices, soy, essential oils nuts, tea, and wine) [13]. They comprise three major phytochemical classes which are phenolic acids, flavonoids and non-flavonoids, based on chemical structures. The most common classes include phenolic acids (including hydroxybenoic acid and hydroxycinnamic acid) and flavonoids (including anthocyanins, flavanols, flavanones, flavones, flavonols, and isoflavonoids) which respectively account for about 30% and 60% of all natural polyphenols. Non-flavonoids are also divided into three subgroups of stilbenes, lignans, and tannins [14]. Due to their potential antioxidant capability, polyphenols are demonstrated to hamper oxidative stress as well as subsequent cellular damages and inflammation [15]. These critical biological functions of polyphenols are ascribed to their exclusive chemical structures. Acting as a potent electron or hydrogen atom donors, owing to possessing aromatic properties and conjugation with numerous hydroxyl groups is one of the polyphenols' unique features. This is extensively contributed to creating a strong defensive obstacle against free radicals and other reactive oxygen species (ROSs) [16]. The active form of polyphenols in plants are glycosides, acylglycosides, and other conjugated forms rather than aglycones [17]. In the human digestive tract, the absorption of phenolic glycosides in foods is less efficient in comparison with their respective aglycones [18]. Therefore, the form of dietary polyphenols may affect the outcome of their health benefits, particularly their antioxidant function [18]. Suppression of oxidative stress-induced damages by polyphenols is also achieved by anti-inflammatory effects of these compounds [17]. It has been reported that polyphenols can inhibit the inflammatory response through interfering with inflammatory signaling cascades, such as nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and possibly through suppression of pro-inflammatory cytokines. These include interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) (p6) [19–,20,21]. Another important function of polyphenols is interaction with basic cellular mechanisms involved in tumor promotion and metastasis, oncogenes, and oncoproteins, including membrane and intracellular receptors, signaling cascades, and basic enzymes (as well as nucleic acids and nucleoproteins). All of the above provide insights into their beneficial health effects [22].

3. Polyphenols: dietary antioxidants that prevent DNA damage

The antioxidant activity of dietary polyphenols involves scavenging free radicals as an electron or hydrogen donating factor [23]. In fact, these compounds potently neutralize the harmful effect of oxygen and nitrogen reactive species including $O2^{\circ -}$, OH°, peroxyl radicals ($RO2^{\circ}$), and peroxynitrous acid (ONOOH) [24,25], as well as perform effective disruption of the propagation phase of lipid autoxidation chain reactions [25]. Increased activity of antioxidant enzymes, such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR), is another function of polyphenols in restoring redox homeostasis [17,24]. In addition to significant upregulation of these enzymes through a nuclear factor erythroid-related factor (Nrf2) modulates the antioxidant-responsive elements (ARE)-mediated transcriptions of various genes, including detoxifying enzymes [17]. Furthermore, these dietary natural compounds protect DNA against the deleterious effects of physical agents, ionizing radiation, and toxins and chemotherapeutic agents. In fact, DNA damage is one of the important, as well as malicious, outcomes of exposure to these agents. Since one of the major causes of DNA damage is the increased ROS levels, the protective effects of polyphenols are probably associated to their antioxidant potential. Table 1 provides a comprehensive list of studies about the protective roles of plant-derived polyphenols, as well as three major classes of these compounds against the DNA damage induced by various agents.

4. Polyphenols modulate DDR

4.1. Polyphenols and DDR sensors

Following any damage to cellular genome, DDR and its key players (DDR sensors) begin to detect and sense DNA lesions. They additionally trigger an intricate cascade to eliminate deleterious damages. DDR sensors recruit the downstream transducer molecules to initiate a kinase-based phosphorylation cascade and elicit an appropriate response for maintaining genome integrity [26,27]. Two distinct protein complexes are involved in the detection of the two major type of single strand breaks (SSBs) and double strand breaks (DSBs) [26]. The DSB sensors involved in the ataxia-telangiectasia mutated (ATM) pathway are MRE11/RAD50/NBS1 (MRN) complex that recruits ATM at the DSB sites, and activates ATM to phosphorylate the target proteins [6]. In addition, the ATM activation triggers one of the earliest events of DDR at the DSB site, namely phosphorylation of the histone-variant H2AX producing γH2AX [6]. γH2AX functions in turn as a signal for DNA damage. Replication protein A (RPA), a single-strand DNA (ssDNA)-binding protein, functions as a sensor in the ATR pathway [28]. In ssDNA damages, replication protein A (RPA) and RAD9/RAD1/HUS1 [9,1,1] act as sensors and activate ATR pathway [28].

4.1.1. MRN complex

A major DDR sensor involved in the DSB recognition and recruitment of downstream transducers, the MRN complex consists of two structurally proteins, namely Mre11 and Rad50, involved in the tethering and trimming of DNA ends. It also has a regulatory component, Nbs1, which is a substrate of the ATM kinase and by activation forms an amplification loop for ATM activation [29]. The current knowledge of the modulatory effects of polyphenols on the DDR through regulation of MRN complex is very small. Gatz et al. [30] examined the effects of resveratrol, a polyphenol belong to stilbenes, on the DSB repair in lymphoblastoid cell lines where resveratrol suppressed DNA repair machinery independently of growth and death regulatory functions. Resveratrol was also shown to phosphorylate the Nbs1 at Ser343. Nbs1, in turn, repressed DNA repair possibly via the MRN complex, suggesting that both ATM and ATR function as Nbs1 kinases activated by resveratrol [30]. In another study evaluating the therapeutic potential of pomegranate extract containing various polyphenols, it was reported that resveratrol inhibited breast cancer cell growth by inducing cell cycle arrest in G2/M, followed by the induction of apoptosis [31]. Cells treated with pomegranate extract resulted in significant down-regulation of proteins encoded by RAD50, NBS, and MRE11 forming the MRN complex, which maintains genome stability during replication and is essential for cell viability. Therefore, polyphenols were shown to affect the DNA repair pathway required for the survival of cancer cells [31].

4.1.2. γH2AX

Plant extract polyphenols: γH2AX foci mark sites of DSB breaks and recruit multiple components of DDR and DNA repair. When the DNA lesions are completely removed, γH2AX is de-activated. However, in cells with unstable genomes, γH2AX remains activated and cells replicate without complete DNA repair [32]. The biomarker of DNA damage, γH2AX is frequently reported to be regulated by DNA damage-inducing genotoxic agents in tumor cell [33]. An increasing number of reports suggest γH2AX to be a potential target of polyphenols in modulating DDR. Polyphenols-induced reduction in DNA damage, as well as decrease in ROS levels are two important factors in restriction of tumor initiation and promotion. *Camptosorus sibiricus* Rupr (CSR) extract, containing high percentage of various polyphenols, was reported to suppress ROS production by re-activating Nrf2-mediated reductases in lung adenocarcinoma cells in the presence of Benzo(a)pyrene (B[a]P) [34]. Moreover, CSR attenuated γH2AX formation and hence reducing the DNA damage of cancer cells. All of the above effects results in

Table 1
Protective roles of various polyphenols against DNA damage.

Polyphenol	DNA damage–induced toxins	Targets	DNA damage evaluation assay	Major finding	Ref.
4-coumaric acid	Ultraviolet B	Rabbit corneal-derived cells (SIRC)	Measurement of 8- OHdG levels	Decreased 8-OH-dg levels; Stabilized SOD activity; Decreased xanthine oxidase activity	[197]
Red wine polyphenols	Oxidant	Colonic mucosa of F344 rats	Comet assay	Decreased the oxidative DNA damage; Suppressed inflammatory response and steroid metabolism	[198]
Polyphenols in Vitis vinifera stem extracts	OH˚ and ROO˚	Liver (hepg2) and cervical (hela) cancer cell	DNA strand cleavage assay	Decreased oxidative DNA damage; Inhibited cancer cell growth	[199]
Polyphenols in extract of Crataegus pinnatifida pollen	H_2O_2	Mouse lymphocytes	Assay and pbr322 plasmid DNA breaks in site specific and non-site specific systems	Decreased oxidative DNA damage; Registered cytoprotection	[200]
Tannic acid and gallic acid, ellagic acid	Cu2 + ions and H_2O_2	B14 Chinese hamster cells	Comet assay	Increased oxidative DNA damage	[201]
Polyphenols in dry olive leaf extract	Adrenaline	Human peripheral Leukocytes	Comet assay	Decreased oxidative DNA damage	[202]
Green tea polyphenols	Cigarette smoke solution, H_2O_2, or $FecCl_3$	LUNG CELLS	DNA microfiltration assay and DNA precipitation assay	Inhibited DNA stand breakage	[203]
Lonicera caerulea and Vaccinium myrtillus fruit polyphenols	Ultraviolet B	Hacat keratinocytes	Comet assay	Reduced in the extent of DNA breakage, caspase-3 and caspase-9 activity, IL-6 expression and DNA laddering	[204]
Punica granatum seed oil polyphenols	Ultraviolet B	Hacat keratinocytes	Comet Assay	–	[205]
Polyphenols in grape juice	2,4,6-trinitrobenzene sulfonic acid	Colonic tissue of Wistar rats	Comet Assay	Decreased DNA damage; Reduced expression of iNOS, TNF-α, and COX-2	[206]
Black soybean seed coat polyphenols	Benzo[a]pyrene	Hepg2 cells and ICR mice	–	Decreased DNA damage; Downregulated P4501A1; Increase the gsts Nrf-2	[207]
Whole honey polyphenols	Oxidant	Mice Lymphocytes	Comet assay Measurement of 8-OHdGlevels	Decreased oxidative DNA damage and 8-OHdG levels	[208]
Wine polyphenols	H_2O_2	Human lymphocytes	Micronucleus assays	Decreased oxidative DNA damage	[209]
Mediterranean plant extracts	H_2O_2	Human lymphocytes	Comet assay	Decreased oxidative DNA damage	[210]
Green tea polyphenol	Ultraviolet B	Human Skin	Immunohistochemical technique using monoclonal antibodies to thymine dimers	Decrease in the formation of thymine dimers	[211]
Caffeic Acid esters and ¯avonoids	Tert-butylhydroperoxide	U937 cells	Comet assay	Decrease in the DNA damage via an iron-chelating mechanism	[212]
Beers polyphenols	Oxidants	Calf thymus DNA	Measurement of 8- OHdG	Protection of DNA oxidative damage decreasing deoxyribose degradation and DNA scission Inhibition of 8-ohdg formation	[213]
Apple extracts polyphenols	ROS	Caco-2 Cells	Comet assay	Diminished DNA damage and ROS Diminished gpx activity	[214]
Polymeric Black Tea polyphenols	[3 H]-B(a)P	Rat liver Microsomes	Measurement of [[3]H]-B(a)P-derived DNA adducts	Decrease in [3 H]- B(a)P-DNA adduct formation due to inhibition of isozymes of CYP450 s	[215]
Flavonoids	H_2O_2	Jurkat cells	Comet assay	Diminished DNA damage and ROS	[216]
Rose myrtle extract polyphenols	Ultraviolet B	Normal human epidermal keratinocytes	Measurement of cyclobutane pyrimidine dimers	Exhibited protection of UVB-induced cytotoxicity Reduced the production of cyclobutane pyrimidine dimers Enhanced the activity of the DNA polymerases	[217]
Polyphenols	Cu and H_2O_2	Plasmid DNA	Comet assay	Diminished DNA damage	[218]
Green tea phenol extracts	Ultraviolet B	KB cells and normal human keratinocytes	ELIZA	Decrease in DNA damage through interleukin-12	[219]
Purple and green husk flavonoids	UV	Plasmicl DNA	Comet assay	Diminished DNA damage	[220]
Honey polyphenols	Pesticide	Bronchial epithelial cells	Comet assay	Efficiently inhibited ROS formation Reduced DNA damage by upregulation of DNA repair through NFR2	[221]
Anthocyanins	Tert-butyl-hydroperoxide	Rat smooth muscle and hepatoma cells	Comet assay	Decreased cytotoxicity, DNA SSB formation and lipid peroxidation	[222]
Anthocyanins	Ultraviolet B	*Centaurea cyanus* Cells	Formation of pyrimidine dimers	Decreased resistance to UV irradiation and the reduced the extent of formation of dimers	[223]
Anthocyanins	Oxidants	Blood samples of healthy probands	Comet assay	Reduced oxidative DNA damage Increased glutathione level	[224]
Anthocyanins	Oxidants	Patients on Hemodialysis	Comet assay measurement of formamidopyrimidine-DNA glycosylase enzyme	Decreased DNA damage, protein and lipid peroxidation Decreased nuclear factor-KB binding activity Increased glutathione level	[225]

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Table 1 (*continued*)

Polyphenol	DNA damage–induced toxins	Targets	DNA damage evaluation assay	Major finding	Ref.
Anthocyanins	Cyclophosphamide	Swiss male mice	Comet assay	Reduction in the frequency of micronuclei in polychromatic erythrocytes Decreased DNA damage	[226]
Anthocyanins	Irinotecan	Colon of Wistar rats	Comet assay	Diminished DNA-strand-breaking activity Suppression of the cleavable complex formation	[227]
Anthocyanins	Topoisomerase I and II Poisons	Colon Carcinoma Cells	Comet assay	Reduced rate of DNA strand breaks	[228]
Anthocyanins	H_2O_2	SH-SY5Y and HL-60 cells	Comet assay	Inhibition of the increase in ROS levels Decrease in DNA damage	[229]
Anthocyanins	Hydroxyl radicals	Calf thymus DNA	Measurement of TBA-reactive substances	Decrease in DNA damage by formation of cyanidin-DNA complex	[230]
Anthocyanins	Benzo[*a*]pyrene	MCF-10 F cells	BP dihydrodiol-epoxide (BPDE)–DNA Adduct quantitation	Inhibition of DNA adduct formation Decrease in ROS levels	[231]
Curcumin	Quartz particles	Rat lung epithelial cell line	Immunocytochemistry for 8- OHdG	Reduced quartz-induced cytotoxicity and cyclooxygenase 2 Inhibited the release of macrophage inflammatory protein-2 Failed to protect the RLE cells from oxidative DNA damage Caused oxidative DNA damage	[232]
Curcumin	Beta-amyloid	PC12 cells	Comet assay	Decreasing the oxidative stress, and DNA damage Attenuated the elevation of intracellular calcium levels and tau hyperphosphorylation	[233]
Curcumin	Benzo(a)pyrene	Male Swiss albino mice	Comet assay Measurement of 8- OHdG levels	Decreased the levels of 8-OXO-dg content	[234]
Curcumin	Oxidants	Livers and kidneys of rats with biliary obstruction	Comet assay	Decreased biomarkers of hepatocellular damage Decreased DNA damage Reduced malondialdehyde and NO levels Enhanced glutathione levels and catalase, SOD, and glutathione S-transferase enzymes activities	[235]
Curcumin	Ferric nitrilotriacetate	Male ddy mice	Immunocytochemistry for 8-OHdG	Abolished the formation of (i) modified Protein adducts, (ii) 8-ohdg, and (iii) protein reactive carbonyl	[236]
Curcumin	Cisplatin	PC12 cells	Comet assay	Decreased DNA damage	[237]
Curcumin	Arsenic	Human lymphocytes	Comet assay Fluorescence-activated DNA unwinding assay	Reduced the DNA damage Retarded ROS generation and lipid peroxidation Raised the level of antioxidant activity	[238]
Curcumin	Methylglyoxal	Human mononuclear cells	Evaluation of DNA strand breaks	Decreased oxidative stress and DNA damage. Inhibited apoptosis and generation of ROS	[239]
Curcumin	Formaldehyde	Male Wistar-Albino rats	Measurement of 8- OHdGlevels	Reduced the levels of sera MDA Increased the TAC, TP53, and beta-amyloid levels	[240]
Curcumin	Perfluorooctane sulfonate	Rat peripheral blood	Micronucleus test Comet assay	Prevented the formation of DNA Damage	[241]
Curcumin	Cisplatin, etoposide, camptothecin, doxorubicin and radiation	Glioblastoma cells	Comet assay	Overcame drug resistance Increased DNA damage Reduced expression of bcl-2 and IAP family members as well as DNA repair enzymes (MGMT, DNA-PK, Ku70, Ku80, and ERCC-1)	[242]
Curcumin	Curcumin	Human Hepatoma G2 Cells	Immunocytochemistry for 8-OHdG Comet assay	Imposed oxidative stress and damaged DNA at high dose of curcumin	[243]
Curcumin	Curcumin- Cu (II)	CCRF-CEM Leukemia Cells	Atomic force microscopy Comet assay	Increased DNA damage	[244]
Curcumin	Propoxur	Human peripheral blood mononuclear cells	Measurement of 8- OHdG levels	Increased GSH Decreased MDA and 8-OH-dg levels	[245]
Curcumin	Phorbol-12-myristate 13-acetate	Mouse fibroblast cells	Measurement of 8- OHdG levels	Decreased 8-OH-dg levels	[246]
EGCG	Ultraviolet and visible radiation	Lung fibroblasts, skin fibroblasts and epidermal keratinocytes	Comet assay	Protected against DNA damage	[247]

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Table 1 (*continued*)

Polyphenol	DNA damage–induced toxins	Targets	DNA damage evaluation assay	Major finding	Ref.
EGCG	Cr(VI)	Jurkat cells	DNA strand breakage assays	Exhibited a protective effect against DNA damage Inhibited activation of nuclear transcription factor NF-kb	[248]
EGCG	Capsaicin	Human erythrocyes and leucocytes	Comet assay	Prevented changes in antioxidant enzyme activities and MDA level and DNA damage	[249]
EGCG	UVA radiation	Hacat cells	Comet assay	Protected against the oxidative cellular and genotoxic damage	[250]
Naringenin	Cisplatin	Rats	Measurement of 8- OHdG levels	Restored biochemical and oxidative stress parameters in serum, renal, and liver tissues Reduced 8-ohdg level	[251]
Hesperidin	Cisplatin	Bone marrow cells of mice	Micronucleus assay	Promoted the reduction of micronuclei frequency and DNA damage	[252]
Apigenin	H_2O_2	Prostate Epithelial cells	Measurement of 8- OHdG levels	Decrease DNA damage Decrease ROS production	[253]
Ipriflavone	Cyclophosphamide	Bone marrow cells of mice	Micronucleus assay	Decrease DNA damage	[254]
Genistein and Daidzein	UVB	BJ-5ta cells	Measurement of Gadd45 Comet assay	Exerted a synergistic photoprotective effect Decrease DNA damage	[255]
Genistein	H_2O_2	Prostate cancer cells	Comet assay	Protected against DNA damage by expression of antioxidative products, Comet assay such as metallothioneins.	[256]
Soy isoflavones	Antileishmanial Glucantime	Swiss mice	Comet assay	Reduced the genotoxicity caused by Meglumine antimoniate. Protective effect against DNA damage is related reduction of oxidative stress	[257]
Isoflavonoids and Lignans	T-BOOH	Hepg2 and MDA-MB-468 Cells	Measurement of 8-OXO-dGlevels	Protected against DNA damage by hydroxyl radical-scavenging, iron-chelating and DNA-binding activity	[258]
Genistein	Polycyclic aromatic hydrocarbon	Non-cancerous breast cells MCF-10A	Comet assay	Decrease DNA damage	[259]
Genistein and Daidzein	Isoflavones metabolites	Estrogen-sensitive breast cancer MCF-7 cells	Measurement of 8-OXO dGlevels	Oxidative DNA damage induced by poltphenols played a role in tumor initiation Proliferation by isoflavones via ER-ERE binding induces tumor promotion and/or progression	[260]
Genistein-8-C-glucoside	H_2O_2	Mouse embryonic fibroblast	Comet assay	Reduced cell viability and Induced DNA damage	[261]
Genistin	UV	Human melanoma cells	Comet assay	Induced plasmid DNA damage And cell growth	[262]
Isoflavone	H_2O_2	Sperm	Comet assay	Reduced DNA damage	[263]
Isoflavones	Sodium nitrite	Mouse stomach	Measurement of 8- OXO-dG levels Comet assay	Increased DNA damage	[264]
Isoflavones	Nitric oxide or peroxynitrite	RAW 264.7 cells	Comet assay	Decreased DNA damage via nitric oxide or peroxynitrite scavenging activities and their prevention of antioxidant enzyme inactivation.	[265]
Xanthohumol	Menadione	Murine hepatoma Cells	Comet assay	Induced DNA damage through induction of quinone reductase	[266]
Resveratrol	1,2-dimethylhydrazine	Rat colon	Comet assay	Increased the enzymic and non-enzymic Antioxidant status Decreasd the extent of lipid peroxidation markers Decreased DNA damage	[267]
Resveratrol	Ageing	Male grey mouse lemur	Measurement of urinary oxidized nucleoside levels	Decreased DNA damage	[268]
Resveratrol	Sepsis	Liver and kidney of rats	Comet assay	Decreased DNA damage	[269]
Resveratrol	Acrylamide	Rats	Measurement of 8-OXO-dG levels	Decreased serum enzyme activities, Cytokine levels and leukocyte late apoptosis Decreased DNA damage	[270]
Resveratrol	Ageing	Hybrid mice	Measurement of 8- OH-dG levels	Reverses pro-inflammatory cytokine profile and oxidative DNA damage	[271]

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Table 1 (*continued*)

Polyphenol	DNA damage–induced toxins	Targets	DNA damage evaluation assay	Major finding	Ref.
Resveratrol	Aflatoxin B1	Human lymphocytes	Measurement of chromosomal aberrations and sister chromatid exchanges	Exerted genoprotective activity on DNA damage	[272]
Resveratrol	UV	Lung cancer cells	Comet assay	Enhanced ionizing radiation-induced premature Increased DNA damage	[273]
Resveratrol	Polycyclic aromatic Hydrocarbon	MCF-10A cells	Comet assay	Decreased DNA damage	[274]
Quercetin and quercetin-rich fruit juice	Benzo(a)pyrene	Human lymphocytes	Comet assay	Protected against chemically induced DNA damage	[275]
Quercetin	Cadmium	Human lymphocytes	Comet assay	Decreased DNA damage	[275]
Quercetin	Alloxan	Type 2 diabetic mice	Comet assay	Protected against hyperglycemia, oxidative stress and DNA damage	[276]
Quercetin or resveratrol	5-aminolevulinic acid	Plasmid DNA	Measurement of 8- OXO-dG levels	Exerted protective action against free radical damage	[277]
Quercetin and rutin	Mitomycin C	Human lymphocytes	Comet assay	Exerted protective action against free radical damage	[278]
Quercetin	Gamma radiation	Human lymphocytes	Comet assay Micronuclei assay	Decreased the genetic damage Improved antioxidant status through its antioxidant potential	[279]
Quercetin	Methylmercury	Rats	Comet assay	Increased GSH and gpx levels Decreased DNA damage	[280]
Myricetin, Quercetin and Rutin	H_2O_2	Caco-2 and Hep G2 Cells	Comet assay	Decreased DNA damage	[281]
Quercetin	2-dimethylhydrazine	Rats liver	Measurement of 8- OXO-dG levels	Decreased DNA damage	[282]
Quercetin	Mercury	Human-derived liver cells	Measurement of 8- OXO-dG levels Comet assay	Decreased DNA damage Modulated oxidative stress	[283]
Myricetin, quercetin, (+)-catechin and (-)-epicatechin	N-nitrosamines	Human hepatoma cells	Comet assay	Protected cells against oxidative DNA damage	[284]
Epigallocatechin gallate and quercetin	A,a-diphenyl-b-picrylhydrazyl	Jurkat T-lymphocytes	Comet assay	Scavenged free radicals Inhibited oxidative damage to cellular DNA	[285]
Quercetin	Etoposide	Bone marrow cells Of rats	Comet assay	Protected cells against DNA damage Increased SOD activity	[286]
Quercetin	Cisplatin hyperthermal intraperitoneal Chemotherapy	Male albino mice of Swiss strains	Comet assay	Protected the blood, liver and Kidney cells of mice against injury Increased survival of mice by improving the antitumor adaptive immunity with hyperthermia.	[287]
Quercetin	Hydroxyl and superoxide Anion radicals	Human leucocytes	Comet assay	Was a more potent inhibitor of hydroxyl radical formation than a scavenger of superoxide anions	[288]

decrease in the tumor volume, tumor size, and multiplicity of B[a]P-induced lung adenocarcinoma, as well as suppression of tumorigenesis by CSR [34]. The flaxseed-derived lignan phenolic secoisolariciresinol diglucoside (SDG) was reported to protect non-malignant lung cells from radiation damage [35]. SDG decreased the radiation-induced accumulation in the DNA damage characterized by decrease in the percentage of γH2AX-positive cell [35]. Similar results were found for mangiferin aglycone against radiation-induced DNA damage on normal human intestinal epithelial cells (HIECs) [36]. It was shown that mangiferin aglycone could eliminate 46.8% of the total DSBs, as marked by decrease in γH2AX formation [36]. Pre-treatment of cells with the extracts could significantly decrease induced DSBs, DNA fragmentation, and intracellular ROS, as well as γH2AX formation compared to non-treated cells [37]. Amararathna et al. [37] for example, reported that polyphenols-rich has kap fruit extracts prevented tobacco specific nitrosamine-induced DNA damage in lung epithelial cells. Green tea catechin suppressed γH2AX formation induced by B[a]P in breast cancer cells [38]. In addition to the chemopreventive function of polyphenols, these compounds attract more attention because of their potential antitumor effects in various cancer cells mediated by the increase in cellular DNA damage and hence induction of apoptosis and other cell death pathways. For example, oleocanthal isolated from extra-virgin olive oil (EVOO) was reported to increase ROS levels, suppress cell growth, and induce apoptosis in liver and colon cancer cell lines [39]. *Leptadenia pyrotechnica* polyphenols decreased the cell viability in colon cancer cells and induced a p53-dependent apoptosis through accumulation of γH2AX and DNA damage [40]. In another study, the effects of *Iraqi propolis* extract on the γH2AX and DNA damage levels was evaluated in colon cancer cell line. It induced apoptosis in HL-60 cells associated with downregulation of Bcl-2 and activation of Bax, stimulated cell cycle perturbations as well causing enhancing γH2AX expression, increase in p53, and decrease in Ki-67 expression of cells in tumor sections [41]. Moreover, oleocanthal treatment induced expression of γH2AX, enhanced and caused mitochondrial depolarization, all of which contributed to therapeutic potential of this polyphenol against cancer cells [39]. In breast cancer cell lines, diosmin, a citrus fruit flavonoid, induced senescence, apoptosis and autophagy [42]. It caused G2/M cell cycle arrest, as well as elevation in p53, p21 and p27 levels. In addition, it increased DNA damage, as indicated by increase in γH2AX expression, hence acting against breast cancer cell lines [42]. In prostate cancer cells, polyphenol piceatannol was reported to inhibit cell proliferation through cell cycle blockade in G1/S and S phases, and apoptosis induction by increasing γH2AX expression, and targeting the mammalian target of rapamycin (mTOR)/AKT signaling [43]. In ovarian cancer cells, polyphenol myricetin induced apoptosis via increasing endoplasmic reticulum stress and γH2AX expression, hence DSBs [44]. In lymphoid leukemia cells, polyphenols reduced ATP levels, inducted apoptosis and increased S and/or G2/M phase cell cycle arrest, hence enhancing doxorubicin and etoposide activity, [45]. Moreover, a combination treatment caused a synergistic downregulation of glutathione levels, increased DNA damage and γH2AX expression, as well as driving apoptosis via caspase-8 and caspase-9 activation [45]. Moron et al., evaluating using comet assay and γH2AX focus assay, showed that chlorogenic acid, a plant polyphenol, induced DNA damage in lung and leukemia cancer cells [46]. They found that this polyphenol induced high levels of topoisomerase I- and topoisomerase II-DNA complexes in cells [46]. Anthocyanin-rich blueberry extracts were also reported to decrease UV-induced ROS levels and lessen DNA damage by tail moment of comet assay and expression of γH2AX *in situ* [47]. Additionally, it significantly downregulated p53 and p21 in UV-irradiated liver cancer cells [47]. Soy bean extract containing genistein induced γH2AX in mouse myeloid progenitor cells, which is dependent on the poisomerase IIβ isozyme and proteasome activity [48].

Curcumin: Curcumin is a major bioactive compound of plan *Curcuma longa* which attracts much more attention in cancer field for its various functions in suppressing the initiation/ progression of various human cancers. It has been demonstrated that it can also modulate DDR components, especially γH2AX. For example, curcumin stimulated γ-H2AX foci in irradiated malignant and transformed MCF-7 cell lines [49]. Additionally, curcumin was shown to suppress cell growth and increase the percentage of cells from G0/G1 with a concomitant increase in G2/M phases, as well as a decrease in proliferating cell nuclear antigen (PCNA) and Rho-A protein expression [49]. In acute promyelocytic leukemia HL-60 cell line, a combination of curcumin and epicatechin resulted in a significant increase in the γH2AX level [50]. Moreover, curcumin can potentiate the DNA damaging effects of various chemotherapeutics, such as etoposide [51] and histone deacetylase (HDAC) inhibitors [52]. Papież et al. [51] showed that curcumin synergistically increased the cytotoxic effect of etoposide, intensified apoptosis and phosphorylation of the histone H2AX in leukemic HL-60 cells. However, curcumin did not significantly modify etoposide-induced cytotoxicity and H2AX phosphorylation in normal CD34+ cells and granulocytes [51]. Saleh et al. noted that both etoposide and curcumin elicited DSB and evoked γH2AX foci formation [53], and that co-treatment with etoposide and curcumin resulted in modulation of the level of DNA damage induction and repair compared with either agent alone In addition, cell cycle analysis revealed S-phase arrest after etoposide and curcumin application [53]. In prostate cancer cells, curcumin exerted a therapeutic function through suppression of cellular proliferation and induction of histone H2AX phosphorylation [54]. More interestingly, curcumin analogues, including bisabolocurcumin ether (T1) and demethoxybisabolocurcumin ether (T2), were also reported to trigger a much stronger apoptosis induction in multiple types of cancer cells than curcumin does, owing to persistent and stronger ROS generation. In addition, ROS induction by T1 resulted in activation of p38/H2AX axis and p53. Inhibition of p38/H2AX led to a significant reduction of apoptosis, whereas inactivation of p53 dramatically enhanced H2AX phosphorylation and apoptosis induction, suggesting that activation of p38/H2AX contributed to apoptosis induction by T1. However p53 activation protected novel curcumin-induced apoptosis via suppression of H2AX activation [55].

Flavanols: Flavanols or flavan-3-ols exist in various forms of monomers (catechins), oligomers, and polymers, displaying the most complex structures among subclasses of flavonoid. The major member of this subclass, (-)-epigallocatechin-3-gallate (EGCG), has been found to exert chemopreventive, as well as therapeutic effects through targeting DDR key components, especially γH2AX. For example, in lung tissue exposed to the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), treatment by EGCG was shown to attenuate DNA methyltransferase 1, p-AKT, and γH2AX inductions, and hence inhibiting lung tumorigenesis [56]. Study on H1299 lung cancer cell lines and xenograft tumors has shown that tumor cell apoptosis and oxidative DNA damage, assessed by the formation of 8−OHdG and γH2AX, were increased by EGCG treatment [57]. Treatment with EGCG also caused the generation of intracellular ROS and mitochondrial ROS [57]. In colorectal cancer cell lines, EGCG induced apoptosis and cell cycle arrest [58]. An increase in DSBs determined by γH2AX protein levels and induction of histone H3 hyperacetylation was additionally observed with the EGCG treatment [58].

Ellagic acid: Ellagic acid, a dietary polyphenol belonging to phenolic acids subclass, is abundantly found in pomegranate, grapes, strawberries and walnuts. This compound was reported to increase the radiosensitization of HeLa cells through induction of γH2AX foci formation, cell growth suppression, cell cycle arrest, disruption in mitochondrial membrane potential and apoptosis induction [59]. In addition to killing cancer cells, the Ellagic acid exerts radio-protective effects on normal cell and aids recovery from the radiation damage [59], as well as enhancing apoptotic radiosensitivity of cervical tumor cells. Induction of apoptosis in HeLa cells is mediated by increased ROS, increased calcium levels, activation of full form (PLC), and decreases in the mitochondrial potential [60]. Furthermore, increased radiosensitivity is mediated by increase in γH2AX foci formation and hence DNA damage in cancer

cells [60]. Similar results have been reported for the effects of this compound on γ-irradiated in human breast cancer MCF-7 cells [61]. Combined treatment of ellagic acid and radiation significantly induced apoptosis, cell cycle arrest, and decreased mitochondrial membrane potential accompanied by an increase in DNA damage and γH2AX expression [61].

Resveratrol: Resveratrol is an anti-fungal phytochemical that belongs to the stilbenes subclass of polyphenols. The major dietary sources of resveratrol include grapes, berries, and red wine. In addition to various biological functions attributed to this polyphenol, an increasing number of studies are pointing to the involvement of resveratrol in the DDR, investigating its effects on the DDR components such as γH2AX. In this context, the function of resveratrol depends on the type of cell and the experimental conditions: in some cell types it decreases DNA damage, while in other cells increasing DNA damage by resveratrol is the favorable effect. For example, it was reported that HS-1793, a resveratrol analogue, effectively suppressed DNA damage in 2 Gy-irradiated Chinese hamster's ovary (CHO)-K1 cells [62]. This effect of HS-1793 was mediated by free radical scavenging and DNA strand breaks inhibition, as indicated by decrease in the levels of phosphorylated H2AX. Moreover, glutathione levels and SOD activity was also increased following HS-1793 treatment. Therefore, HS-1793 was proposed to have chemical radioprotective activity [62]. In Jurkat T cells treated with camptothecin, resveratrol metabolites resveratrol-3-*O*-glucuronide, resveratrol-4′-*O*-glucuronide decreased DSB as well as the expression levels of γH2AX. In other words, the metabolites decreased DNA damage induced by camptothecin [63]. However, other investigations have reported contrasting results as to resveratrol may increase DDR in combination with other chemotherapeutics, and radiation, or even alone. Li et al., reported that resveratrol induced cell cycle arrest and cellular senescence in U2OS and A549 cancer cells as well as in normal human fibroblasts [64]. This effect is believed to be mediated by the elevation of ROS induced DNA damage and increase in the amount of γH2AX. The authors additionally demonstrated a critical role for p53-CXCR2 axis in mediating resveratrol-induced senescence. In human primary dermal fibroblasts (BJ), resveratrol increased the senescence in association with β-galactosidase activity and methylated H3K9-Me. Additionally, resveratrol treatment also resulted in significant increase in phosphorylation of γH2AX, as well as levels of p53, $p21^{CIP1}$ and $p16^{INK4A}$ [65]. In another in vitro study on the human chronic myelogenous leukemia cells, resveratrol induced apoptosis and phosphorylation of H2AX [66]. In addition, resveratrol treatment activated two MAPK family members (p38 and JNK) and blocked the activation of another MAPK family member ERK. Overexpression of H2AX in cancer cells markedly increased resveratrol-induced apoptosis, whereas overexpression of H2AX-139 m (Ser139 was mutated to block phosphorylation) inhibited resveratrol-induced apoptosis. K562 cells transfected with H2AX-specific siRNAs were resistant to resveratrol-induced apoptosis [66]. Some recent studies report that DDR suppressive effects of resveratrol are concomitant with the inhibition of the topoisomerase IIa. Leone et al. [67,68] reported that resveratrol treatment of human glioblastoma cells induced cell cycle arrest in addition to increase in histone H2AX phosphorylation. Therefore, resveratrol could be considered a topoisomerase IIa poison. Rashid et al. [69] investigated the effects of resveratrol on the radiation sensitivity of prostate cancer cell lines. The authors reported that this polyphenol inhibited survival of cancer but not normal prostate cells. In addition, it was observed that H2AX phosphorylation and DNA damage increased in cancer cells treated with resveratrol; hence a significant induction was resulted in radiation-induced cell cycle arrest, nuclear aberrations and apoptosis. Similar results were reported in a study by Basso et al. [70] in which resveratrol-pretreated human lymphocytes showed higher expression of γH2AX in irradiated cells. An increase in γH2AX levels and consequent DNA damage is the main mechanism of resveratrol treatment in combination with other agents, such as purine analogues [71], temozolomide [72], metformin [73], and pterostilbene in suppressing various cancer cells proliferation [74].

4.2. Polyphenols and DDR transducer

DDR transducers are responsible for the amplifying and transmitting signals form sensors to mediators [75]. The serine/threonine kinases, ATM and ATR, are well-known transducers in the DDR pathway, initiating a cascade of phosphorylation events following DNA damage [76]. Upon DSBs, the inactive ATM dimer is stimulated by monomerization and eventual intermolecular phosphorylation of multiple serine residues. At ssDNA lesion sites, ATR-interacting protein (ATRIP), which binds to the RPA-ssDNA complex, recruits ATR [76]. Both ATM and ATR phosphorylate mediator proteins, such as the breast cancer susceptibility gene 1(BRCA1), NBS1, p53, CHK1, and CHK2 ATM kinases, also phosphorylate Chk2, p53, and BRCA1in order to transmit the damage signals to effectors and elicit appropriate response [77]. While knockout ATM mutations result in pleiotrobic defects, such as growth defects, infertility, and neurologic dysfunction, an ATR mutation results in embryonic lethality [77]. DNA-dependent protein kinases (DNA-PKcs) are induced upon the detection of DSBs and subsequently autophosphorylate and phosphorylate other substrates. DNA-PKcs play an important role in DSB repair through non-homologous end joining (NEHJ) [78]. An accumulating body of studies has reported DDR transducers as potential targets of various subclasses of polyphenols. George et al. [79] showed that apple flavonoids effectively depressed cisplatin- and methotrexate-induced DNA damage in normal human bronchial epithelial cells, and carcinogen treatment resulted in augmentation of DDR signaling and ATR phosphorylation. Apple flavonoids downregulate DNA-PKcs protein and phosphorylation of ATR, as well as induce a significant inhibition of γ-H2AX protein in flavonoids-pretreated cells. Therefore, pretreatment with phosphorylation of ATR significantly attenuates the DDR proteins specially challenged against carcinogens induced genotoxicity. Biechonski et al. [80] evaluated the effects of quercetin, as an flavonol, on DDR by targeting transducers in human hematopoietic stem as well as progenitor cells. Quercetin activated ATM by triggering its autophosphorylation on Ser1981. ATM activation correlated with a large increase in the proportion of γH2AX-positive cells, confirming DSB accrual. On the other hand, DNA damage produced by quercetin did not trigger the Ser2056 autophosphorylation that would efficiently be triggered by radiation. However, robust DNA-PKcs autophosphorylation on Ser2056 exceeded that of radiation alone, suggesting that quercetin does not inhibit DNA-PK kinase. Thus, quercetin would exhibit genotoxic effects in human hematopoietic stem cells when applied continuously and at high concentrations. In another study by Ye et al. it was demonstrated that genistein induced the phosphorylation of p53 and that genistein-induced accumulation and phosphorylation of p53 was reduced in ATM-deficient human cell lines. In addition, genistein induced the phosphorylation of ATM and histone H2AX. Like genistein, quercetin also induced phosphorylation of ATM, and ATM-dependent phosphorylation of histone H2AX. However, p53 accumulation and phosphorylation occurred in ATM-deficient cells, indicating that ATM is not required for quercetin-induced phosphorylation of p53. Genistein-mediated DDR activation is highly ATM-dependent but in the case of quercetin, may be ATM-dependent only for some downstream targets. Several therapeutic effects of curcumin were also reported to mediate by ATM-dependent induction of DNA damage. For example, Hu et al. [81] reported that curcumin treatment of head and neck squamous cell carcinoma cell lines resulted in the induction of cell cycle arrest and apoptosis through ATM/p53-dependent pathway. In prostate cancer cell lines, the treatment of curcumin effectively suppressed cellular proliferation and induced phosphorylation of ATM, histone H2AX, Chk2, and p53 [54]. Sahu et al. [82] demonstrated that treatment of human pancreatic cancer cells with a low and single concentration of curcumin resulted in significant arrest of cells cycle and induced significant apoptosis. Normal immortalized human pancreatic ductal epithelial cells remained unaffected by curcumin

treatment. These effects of curcumin are believed to be mediated by increased phosphorylation of H2AX and decreased DNA polymerase-b level. In addition, curcumin cytotoxicity is ATM dependent, such that silencing ATM expression by specific SiRNA blocks the phosphorylation of ATM, protecting the cells from curcumin-mediated G2/M arrest and apoptosis. In the vascular smooth muscle cell, curcumin induced senescence in DNA damage and ATM-independent manner, because ATM silencing does not reduce the number of senescent cells [83]. Amin et al. noted that combination of luteolin and EGCG at low concentrations synergistically increase apoptosis in both head and neck and lung cancer cell lines induced by ATM- dependent phosphorylation of p53. In prostate carcinoma DU145 cells, the ATM pathway plays a critical role in gallic acid–induced cell cycle arrest. Activation of DDR evidenced by increased γH2AX that is phosphorylated by ATM in response to DNA damage, triggers antitumor activity of gallic acid in prostate cancer cells [84]. In addition to gallic acid, resveratrol also exerted its anticarcinogenic activities, such as induction of apoptosis [85,86], cell cycle arrest [87], and entrance to senescence state via activation of ATM-dependent DDR in various cancer cells [88]. More importantly, ATM is a direct target of resveratrol. Direct stimulatory effects of resveratrol on purified ATM in vitro increased the catalytic efficiency of the kinase on a model substrate mediated by resveratrol.

4.3. Polyphenols and DDR mediators

Mediator proteins are another key player activated in response to DNA damage, responsible for synchronizing the temporal-spatial control of the multiple factors in the DDR, promoting their activation, as well as recruiting other components, and regulating their association with damaged DNA. Checkpoint kinase 2 (CHK2), mediator of DNA-damage checkpoint protein 1 (MDC1), BRCA1, and p53-binding protein (53BP1) are largely active in the ATM pathway, whereas CHK1, DNA topoisomerase 2-binding protein 1 (TopBP1) and CLASPIN co-regulate the ATR-dependent DDR pathway [89].

4.3.1. 53BP1

53BP1 is a well-known DDR mediator, which is recruited by γH2AX to nuclear structures following DNA damage. This protein is required for processing of the DDR signal and as a platform for recruitment of other repair factors [90]. Among various polyphenols, the effects of curcumin on DDR mediator protein, 53BP1, have been extensively investigated in various cells under DNA damage conditions. Mosieniak et al. for example, reported that curcumin resulted in mitotic disturbances leading to growth arrest and induction of senescence phenotype in human colon and breast cancer. The upregulation of γH2AX as well as a gradual increase in the level of p53 and p21 proteins was also detected. Increase in γH2AX activated 53BP1 foci formation, as well as DDR cascade to curcumin-induced anticarcinogenic function. Dimethoxy curcumin, a metabolically stable analogue of curcumin, was reported to enhance the radiosensitivity of lung cancer cells, through induction of DNA damage, as indicated by significant increase in γH2AX and 53BP1 foci [91], resulting in oxidative stress-induced cell death in human aortic smooth muscle cells, Curcumin treatment increased the number of 53BP1 foci, and promoted disequilibrium of cellular redox homeostasis leading to protein carbonylation and oxidative DNA damage. DNMT2 upregulation was also a part of cellular stress response after curcumin treatment [92]. Similar results were reported for the effects of curcumin in human cells building the vasculature, in which this polyphenol reportedly elevated sirtuin level, DNA damage and 53BP1 foci formation, culminating in postponement of cells senescence [93]. In the case of resveratrol, it was demonstrated that this natural compound significantly inhibited DNA damage- induced apoptosis (decrease in H2AX and 53BP1 phosphorylation) in the cartilage of untreated ACLT plus Mmx rats [94], whereas increased the radiosensitivity of prostate cancer cell lines through an increase in the co-localization of γ-H2AX and 53BP1 foci and hence DNA damage [95]. Naringin and hesperidin treatment caused a robust activation of 53BP1 in response to DNA damage and apoptosis in prostate cancer cell lines [96]. Echinacoside, a hydrophilic polyphenol glycoside, induced apoptosis through enhancement in oxidative DNA damage, as shown by an increase in intracellular oxidized guanine, 8-oxo-dG, and dramatic upregulation of the DSB-binding protein 53BP1 [97]. Genistein induced the phosphorylation of H2AX and the accumulation of 53BP1, hence preventing the formation of excess radiation-induced centrosomes via p21 upregulation in human U2OS cells and mouse NIH3T3 cells [98]. Quercetin exposure resulted in a prolonged presence of radiation-induced γH2AX and 53BP1 foci, as well as increasing the radiosensitivity both in vitro and in vivo [99].

4.3.2. Chk1/2

From a structural point of view, checkpoint kinase 1 (Chk1) and Chk2 are two different molecules, despite having nominal similarity [100,101]. While both kinases are demonstrated to act on the DDR pathway, Chk1 is suggested to be the major kinase responsible for responses to DNA damage [102]. Checkpoint abrogations, suppression of DNA repair and apoptosis induction are various important consequences of genotoxic stress-mediated Chk1 inhibition [103–105]. Several polyphenols target Chk1 and Chk2/ in the process of exerting their therapeutic function. For example, isoliquiritigenin, a natural flavonoid found in licorice, shallots, and bean sprouts, induced cell cycle arrest in both the G2 and M phases via DSB-mediated ATM/Chk2 signaling in HeLa cells [106]. A study has shown that isoliquiritigenin treatment induced ATM and Chk2 phosphorylation, as well as the formation of c-H2AX foci in the nuclei. However, Chk1 phosphorylation did not occur after 8 h of the treatment [106]. Expressions of γH2AX, ATM, Chk2 and p53 are expected to increase following co-treatment with radiation and resveratrol compared with the mock-treated control group in prostate cancer cell lines. This resulted in delayed repair of radiation-induced DSB and prolonged G2/M arrest, which induced apoptosis [95]. Curcumin sensitized various cancer cell lines to poly (ADP-ribose) polymerase (PARP) inhibitors by enhancing apoptosis and mitotic catastrophe. This effect is mediated by impairment in activation of ATR-Chk1 signaling, since the curcumin treatment significantly suppressed the phosphorylation of ATR and Chk1 but not Chk2 phosphorylation, reflecting ATM-Chk2 signaling [107]. In animal model of triple- negative breast cancer, it was reported that gallotannin mediated S-phase arrest and tumor growth inhibition by Chk2 activation. Gallotannin specifically stimulated a dramatic increase of Chk2 phosphorylation, but not of Chk1. Inhibition of Chk2 by specific inhibitor reduced the forced accumulation of cells in the S-phase by gallotannin, indicating that the accumulation of cells in S-phase after gallotannin exposure was due to Chk2 activation [108].

4.3.3. BRCA1

The phosphorylation of BRCA1 plays a critical role in DDR. Following DNA damage, BRCA1 is dispersed from the S-phase foci and relocalized to damage-induced foci. The phosphorylated histone H2AX significantly overlaps with BRCA1 following DNA damage. Therefore, BRCA1 damage-induced foci are thought to be sites of DNA repair [109]. Because of this important function of BRCA1 in DDR, dysfunction in BRCA1, which based on various studies, is mediated by polyphenol compounds, makes cancer cells more susceptible to apoptosis alone or in combination with DNA damaging drugs. Chen et al. [110] showed that curcumin increases the proliferation inhibitory effect of cisplatin and promotes cisplatin-induced apoptosis in resistant lung adenocarcinoma cells. These effects of curcumin were believed to be associated with downregulation of FANCD2/BRCA pathway DNA damage repair processes. Curcumin in combination with cisplatin could exert a synergistic cytotoxic effect in cancer cells. Curcumin induced DNA damage in triple-negative breast cancer cells in association with phosphorylation, increased expression and cytoplasmic retention of the BRCA1 protein, as well as to promote apoptosis and prevent anchorage-

independent growth and migration of triple-negative breast cancer cells. In addition, resveratrol induced the growth arrest of osteosarcoma and lung adenocarcinoma cancer cell lines through upregulation of BRCA1 formed foci, and induction of telomeric instability [111]. Increase in DNA damage by resveratrol also manifested in the phosphorylation of histone H2AX [111]. In breast cancer, soy polyphenols were reported to modulate the signaling pathways in the downstream of BRCA1 and BRCA2 oncosupressor genes [112], as well as the DNA methylation of these genes [113].

4.4. Polyphenols and DDR effectors

DDR effectors receive information about DNA damage via signal transduction through upstream transducers, and after processing, elicit the most appropriate responses by either cell cycle arrest, recruitment of DNA repair machinery, or induction of apoptosis [114]. Surprisingly, previous studies have revealed over 700 proteins in the downstream of transducers phosphorylated by ATM and ATR [76], as well as a large number of novel connections and pathways downstream of some effectors, which have not previously been implicated in DDR. These pathways play a variety of functions, including induced RNA splicing, the spindle checkpoint, mitotic spindle and kinetochore proteins, nonsense mediated decay, tumor suppressors, chromatin remodeling, insulin signaling, and a multitude of transcription factors [114]. All these connections have emphasized one important fact: the role of DDR in cellular physiology is much more than previously appreciated.

4.4.1. Effectors for cell cycle arrest

The major role of the well-orchestrated cell cycle checkpoints is creation of a tight coordination between DNA repair pathway and cell-cycle progression [115]. Following DNA damage and signaling through DDR, a delay or arrest at critical points of cell cycle is induced, either before or during DNA replication or before cell division, through important effectors involved in this stage [6]. Several important DDR effectors with cyclin-dependent kinase (CDK) inhibition function include, p21, a primary regulator of p53-mediated G1 arrest, WEE1 kinase, the key inhibitor of mitotic entry and CDC25 phosphatases (CDC25A, CDC25B, CDC25C) that removes inhibitory phosphorylation on CDK are among the [116]. After DNA damage, CDC25 s are phosphorylated and hence inactivated by Chk1 and Chk2 kinases in order to arrest the cell cycle [116]. Intestinally, induction of cell cycle arrest is a common consequence of treatment of various cells with polyphenols reported in an accumulating body of studies for almost all classes of these natural compounds.

Plant extracts polyphenols: Prasad et al. [117] reported that induction of DNA damage and activation of cell cycle arrest-related effectors were the underlying mechanisms by which polyphenols from green tea effectively suppressed the growth of melanoma cells. These polyphenols induced cell cycle arrest at the G1 phase through inhibition of cyclin D1, cyclin D2 and cyclin E, as well as the expression of CDK2, CDK4 and CDK6 proteins. In colon cancer cell lines, gallotannin was noted to induce senescence independently of p21 and p53. This effect was mediated by gallotannin-induced increase in the generation of ROS and alternation in the redox balance in the cells. Cell cycle arrest at S-phase through induction of DNA damage, as indicated by p-H2AX staining, is another major function of gallotannin on colon cancer cells [118]. Park et al. (106)showed that induction in cell cycle arrest at G2 and M phase is a major therapeutic effect of isoliquiritigenin in human cervical cancer cells mediated by increase in DNA damage-dependent signaling through ATM/Chk2. On the other hand, treatment with isoliquiritigenin inhibited the metaphase/anaphase transition and at the same time it increased the formation of γH2AX foci, the phosphorylation of ATM and Chk2, separate poles and mitotic metaphase-like spindles with partially unaligned chromosomes. The results of another study by Shen et al. [119] showed that chalcone, the precursor compound for flavonoid synthesis in plants, inhibited the proliferation of human bladder cancer cell lines by blocking cell cycle progression in the G2/M phase. More importantly, chalcone significantly increased the expression of p21 and p27 proteins, and decreased the levels of cyclin B1, cyclin A and Cdc2, thereby contributing to cell cycle arrest. In colon cancer cell lines, 5-methoxyflavanone was demonstrated to inhibit the growth and clonogenicity of cancer cells through activation of DDR, as marked by the accumulation of p53 and the phosphorylation of ATM, Chk2, and histone H2AX. Downstream of these events, this polyphenol was reported to induce cell cycle arrest at G2/M phase. Pretreatment of cancer cells with the ATM inhibitor increased 5-methoxyflavanone-induced γH2AX formation, indicating that ATM/Chk2 checkpoint pathway acts as a survival program to block apoptosis induced by this compound [120]. In HaCaT keratinocytes, EGCG reduced the protein levels of cyclin D1 and Zac1 (a zinc-finger protein which regulates apoptosis and cell cycle arrest 1), also induced the expression of p21 and DEC1 (differentiated embryo-chondrocyte expressed gene 1), hence promoting G1 arrest of cell cycle [121]. Naringenin also reported to exert its therapeutic effects through induction of cell cycle arrest and regulation of various effector proteins involved in this event [122,123]. Some polyphenols increase the sensitivity of cancer cells to conventional chemotherapeutic agents by modulation of cell cycle programs. For example, crude phenolic extracts from extra virgin olive oil was indicated to reverse breast cancer resistance to HER1/HER2-targeting drugs by inducing GADD45-sensed cellular stress, G2/M arrest and hyperacetylation of histone H3. This effect was also accompanied by increase in DNA damage [124]. In another study evaluating the effects of scutellarin on prostate cancer cells, researchers found that this polyphenol enhanced the sensitivity of cells to cisplatin, with additional observation that scutellarin suppressed cell proliferation by promoting G2/M arrest and inducing apoptosis, as well as increase in the phosphorylation of H2AX and the downregulation of cell cycle regulatory genes including Cdc2, and cyclin B1 in prostate cancer cells [125]. In several leukemia cell lines, combination of 5-fluorouracil with quercetin, apigenin and rhein caused synergistic decrease in ATP levels, induction of cell-cycle arrest at S-phase and increase in induced DNA damage [126]. EGCG significantly and synergistically enhanced the antitumor effects of the docetaxel in lung cancer cells through induction of G2/M arrest [127].

Genistein: Arrest in cell cycle is also the main underlying mechanism in suppression of cancer progression in the case of genistein. In an important study by Rabiau et al. [128] the effects of genistein on a panel of genes implicated in cell cycle was evaluated by polymerase chain reaction arrays in human prostate cancer cell lines. They reported the upregulation of *CDKN1A* gene, a major cyclin-dependent kinase inhibitor. This gene encodes the $p21^{CIP1}$ protein, which is involved in the regulation of the cell cycle at both the G0/G1 and G2/M phases. *CCNH* (cyclin H), a regulatory component of the cyclin-dependent kinase (CDK)-activating kinase (CAK) was observed to be upregulated in cells treated with genistein. Downregulation of *CHEK2* and *TP53* occurs in cancer cells treated with genistein. This explains the genetic defects of *CHEK2* and *TP53* implicated in prostate cancer development [128]. Working on colon cancer cell lines, Han et al. [129] showed that genistein significantly suppressed cell proliferation through modulation of cell cycle distribution, and resulted in the accumulation of cells at G2/M phase, with a significant decreasing effect of cyclin B1 and Chk2 proteins expression. In a similar study, Constantinou et al. [129] showed that genistein delayed the G2/M phase of the cell cycle, and induced apoptosis of human breast adenocarcinoma MCF-7 cells. Tsuboy et al. [130] working on the same cells, found that supraphysiological levels of genistein (50 and 100 μM) were cytotoxic to these cell lines and induced apoptosis. However, G0/G1 delay of MCF-7 cells were occurred at physiological concentrations of genistein [130].

Quercetin: Quercetin displays a variety of dose-dependent chemopreventive, anti-tumor, anti-oxidant and anti-inflammatory activities [131]. The concentration–response of DNA-damage pathway to this compounds have been evaluated in HT1080 cells (a human cell line

with wild-type p53) at doses relevant to human exposure [132]. Quercetin (20–30 μM) caused ROS generation, DNA damage (measured as phospho-H2AX) and p53 induction. Moreover, it delayed cell cycle at S-phase at low doses (8 μM), suggesting that quercetin affects DNA-damage, p53 response and genotoxicity differently based on the applied. In an study by Jeong et al. [133], it was reported that a low concentration of quercetin exerted cancer cell-specific inhibition of proliferation resulted from cell cycle arrest at the G1 phase [133]. In fact, quercetin induced p21 CDK inhibitor with a concomitant decrease of phosphorylation of pRb, which in turn inhibited the G1/S cell cycle progression by trapping E2F1. Low concentration of quercetin induced mild DNA damage and Chk2 activation, which is the main regulator of p21 expression by quercetin. In addition, quercetin downregulated the cyclin B1 and CDK1, essential components of G2/M cell cycle progression. In breast cancer cell lines, quercetin treatment resulted in the accumulation of cells specifically at G2/M phase of the cell cycle accompanied by a transient increase in the levels of cyclin B1 and CDC2 kinase activity. Moreover, quercetin markedly increased Cdk-inhibitor $p21^{CIP1/WAF1}$ protein level, however, upregulation of p53 by quercetin was not observed. Accordingly, quercetin induced growth inhibition in the human breast carcinoma cell lines by inhibiting cell cycle progression through transient M phase accumulation and subsequent G2 arrest [134]. In addition, cytotoxic effects of quercetin in leukemic cells are also dose concentration-dependent. Quercetin causes S-phase arrest during cell cycle progression in tested cancer cells. Quercetin induced tumor regression and increased the life span in tumor-bearing mice [135].

Resveratrol: Joe et al. [136] reported that resveratrol significantly inhibited the tumor cell proliferation through induction of S-phase arrest in various cancer cell lines, including esophageal adenocarcinoma, colon carcinoma and breast carcinoma, esophageal squamous carcinoma, as well as promyelocytic leukemia cells. The treatment epidermoid carcinoma cells with this polyphenol caused significant suppression of cell proliferation through a G1-phase arrest of the cell cycle. This function of resveratrol was revealed to be mediated by induction of WAF1/p21, decrease in the protein expressions of cyclin D1, cyclin D2, and cyclin E, and decrease in the protein expressions of CDK2, CDK4, and CDK6 [137]. Similar results have been found in prostate cancer cell lines. Kuwajerwala et al. [138] showed that resveratrol resulted in increase in DNA synthesis and enrichment of cancer cells in S-phase, and concurrent decrease in the nuclear $p21^{Cipl}$ and $p27^{Kip1}$ levels. Moreover, nuclear Cdk2 activity increased in association with both cyclin A and cyclin E. In general, prostate cancer cells treated with resveratrol were shown to enter S-phase, but subsequent progression through S-phase is impeded by the inhibitory effect of resveratrol on DNA synthesis. Furthermore, resveratrol treatment was reported to induce S/G2 arrest in cultured bovine pulmonary artery endothelial cell [139], Sphase arrest in articular cartilage of ACLT plus Mmx rats [94], G2/M arrest in cells with mutated human c-Ha-Ras [140], S-phase arrest in glioblastoma cells [68], G1 and S arrest in lung cancer cells [73], and G2/M phase arrest in oral squamous cell carcinoma cells [141]. In diffuse large B-cell lymphoma cells, pterostilbene, a natural demethylated analog of resveratrol, exhibited a strong cytotoxic effect, through significant decrease in mitochondrial membrane potential and also by enhancements in ROS levels, leading to arrest in the S-phase of the cell cycle [142]. In a study by Min et al. [143] the therapeutic function of xanthohumol was evaluated on apoptosis-resistant human Burkitt lymphoma cell line, Raji cells [143]. The authors stated that this polyphenol can efficiently suppress cancer cell proliferation through induction of increase in ROS levels, and subsequent increase in DNA damage. Another major effect of xanthohumol was cell cycle arrest at G0/G1 phase correlated with downregulation of CDK4, cyclin E, phosphorylated cyclin E, and Cdc-2, and upregulation of cyclin-dependent kinase inhibitor P21, all in a P53-independent manner.

Curcumin: Like other polyphenols, induction of cell cycle arrest is an important mechanism for curcumin to suppress cancer cell proliferation. This effect has been further studied in colorectal cancer. In COLO 320DM cell lines, curcumin resulted in the cell cycle arrest at the G0/G1 phase via suppressing the expression or activation of CDK4/6/cyclin D and phosphorylation of Rb [144]. In HCT116 cells, curcumin significantly induced the amount of DNA damage and mediated S and G2/M phase arrest. The cell cycle arrest was hardly reversed by caffeine as an inhibitor of ATM/ATR, indicating that the ATM and ATR signaling pathways may not be involved in curcumin-mediated S and G2/M phase arrest in HCT116 cells [145]. In another study on eight colorectal cancer lines, including Caco-2, DLD-1, HCA-7, HCT116p53+/+, HCT116p53–/–, HCT116p21–/–, HT-29 and SW480, it was reported that the majority of cell cycle arrest occurred at the G2/M transition, with a proportion of cell-arresting in mitosis, following treatment with curcumin [146]. Pre-treatment with inhibitors of the DDR alleviated curcumin-induced mitotic arrest but had little effect on G2/M boundary. Moreover, pH2AX staining seen in mitotic, but not interphase, cells suggests that this aberrant mitosis results in DNA damage [146]. In colon and breast cancer cell lines, curcumin led to mitotic disturbances, cells arrested in mitosis through induction of DSB damage that brought about senescence in cancer cell. On the other hand, inhibition of tDDR by caffeine leads to the attenuation of senescence induction in curcumin-treated cells [147]. Recently, it was shown that curcumin treatment of hepatoma cells results in activation of Chk1-mediated G2 checkpoint, associated with the induction of G2/M arrest and the resistance of cancer cells to curcumin-induced apoptosis [148]. More interestingly, inhibition of Chk1 significantly abrogated G2/M arrest and sensitized curcumin-resistant cells to apoptosis via upregulation of Bad and in turn the loss of mitochondrial membrane potential. The number of studies evaluating the role of curcumin in the regulation of cell cycle and proliferation of cancer cells is growing with the consensus that curcumin imposes cell cycle arrest through modulation of DDR [149–157]. Curcumin treatment resulted in cell cycle arrest at G1 phase in the mesothelioma cell lines [150], G2/M phase in hepatocellular cell lines [151,154], papillary thyroid carcinoma cell lines [152], breast cancer cells [157], and bladder cancer cell lines [155], G0/G1 phase in hepatic stellate cell [153], G0 phase in mammary epithelial carcinoma cells, prostate cancer cell lines, and B cell lymphoma cells [158].

4.4.2. *Effectors for DNA repair*

There are several DNA repair mechanisms for responding to multiple types of DNA damage induced by various agents. A central DDR factor, p53, is involved in the promotion of genomic stability and integrity trough regulation of DNA repair pathways, such as nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end-joining (NHEJ). Components of these DNA repair pathways are mostly regulated by polyphenols. In other words, various polyphenol compounds regulate DNA repair machineries in response to DNA damaging agents and conditions, such as UV-irradiation [99,159–164], oxidative stress [160,165–169], and tert-butyl hydroperoxide [170], as reported by various studies.

4.4.2.1. MMR. Mismatches that happen during meiosis and mitosis are repaired with help from the MMR pathway. That is, the MMR pathway is activated when replication errors, such as insertion/deletion loops (IDLs) occur as a consequence of temple slippage, or base-base mismatches due to DNA polymerase misincorporation of nucleotides [171]. In addition, the MMR pathway acts to repair mismatches generated by spontaneous deamination of 5-methylcytosine as well as heteroduplexes generated subsequent to genetic recombination [171]. Additionally, it has a possible role in antibody class-switch recombination and oxidative DNA damage fixation [171]. Defects in this pathway causes to increase probability of spontaneous mutations and microsatellite instability (MSI) [172]. Mutations in multiple human MMR genes lead to high susceptibility to diseases and different types of

tumors. The three proteins essential for recognition and repair of mismatches are MutS that forms a dimer to detect the mismatched base and binds to mutated DNA, MutH which binds at hemimethylated sites and become activated by a MutL dimer which acts as a mediator between MutS2 and MutH through binding to the MutS-DNA complex [172]. Jiang et al. [173] showed that the MMR system modulates curcumin sensitivity through induction of DSB and activation of G2-M checkpoint. However, the DDR induction was observed to be more considerable in MMR-proficient as compared with MMR-deficient cells. These results indicate that curcumin triggers the accumulation of DNA DSB and induce a checkpoint response through a MMR-dependent mechanism, such that in MMR-deficient cells, curcumin-induced DSB is significantly blunted. As a result, cells fail to undergo cell cycle arrest, enter mitosis, and die through mitotic catastrophe. In lung cancer cell lines, curcumin increased DNA damage and decreased DNA repair in order to suppress cancer cells proliferation. These effects of curcumin on DNA repair capacity of cancer cells were found to be mediated by the inhibition of MMR genes, such as O6-methylguanine-DNA methyltransferase (MGMT), and other genes, including BRCA1, and mediator of DNA damage checkpoint 1 (MDC1) [174]. In addition to curcumin, gallic acid also modulates MMR DNA repair pathway in human oral cancer cells. Weng et al. [175] demonstrated that gallic acid inhibited the protein expressions of MDC1, MGMT, p-H2AX, p53, DNA-PK, and 14-3-3 proteins sigma (14-3-3σ) but increased the amount of ATM, ATR, and BRCA1. That is, gallic acid induced cell death by increase in DNA damage and suppression of DNA repair-associated protein expression in cancer cells [175]. The exact same results were reported by Liu et al. [176] who investigated the effects of gallic acid on prostate cancer cell lines and found that increased DNA damage and decreased DNA repair were essential for chemopreventive effects of gallic acid in prostate cancer.

4.4.2.2. BER and NER. The BER pathway has been developed to manage the high level of spontaneously corrupted products formed in DNA, as well as the injuries that are created by reactions with natural endogenous chemicals, especially ROS [177]. BER is an effect of the action of five important proteins: DNA glycosylases that recognize and remove the damaged base from the sugar-phosphate backbone and leave an apurinic/apyrimidinic (AP) site, AP endonucleases which incise an AP site to produce a 3′-hydroxyl next to a 5′-deoxyribosephosphate (dRP) [177], polynucleotide kinase-phosphatase (PNKP), which assists formation of a hydroxyl on its 3′-end and a phosphate on its 5′-end of DNA strand break, DNA polymerases that help to fill the gaps by inserting a single nucleotide, and DNA ligase which seals the nick. BER machinery is a target of some polyphenolic compounds; some have been reported to increase BER proteins and other have been shown to suppress this pathway in order to function as a chemopreventive agent [178]. For example, Gao et al. [179] showed that exposure of prostate cancer cells to naringenin leads to significant decrease in 8−OH-dG levels, hence DNA damage with significant activation of the BER pathway, as indicated by considerable enhancement in the expression levels of two major enzymes in the this pathway, including 8-oxoguanine-DNA glycosylase 1 (OGG1), and AP endonuclease. Naringenin exerted these effects at its physiological concentrations. Therefore, this polyphenol could prevent mutagenic changes in prostate cancer cells through increment of BER pathway. Interestingly, in a study by Silva et al. [180] it was revealed that some polyphenols, such as luteolin and quercetin, act on the intracellular mechanisms responsible for DNA repair, rather than by a direct effect on ROS scavenging. They also found that rosmarinic acid target OGG1 directly and increases its expression [180]. On the other hand, soy isoflavones was found to sensitize lung cancer cell lines to radiation by increasing DNA damage and suppressing DNA repair. Soy isoflavones and radiation caused an increase in γH2AX foci, indicating both increased DNA damage and inhibition of repair [181]. Soy isoflavones inhibits the radiation-induced activity of the DNA repair/redox enzyme APE1/Ref-1. Methoxyamine, which in turn inhibits APE1/Ref-1 DNA repair activity with incomplete blockade of the decrease in radiation-induced DSBs, displays partial mitigation of radiation-induced DNA repair akin to the effect of soy combined with radiation [181].

NER is an extremely significant and versatile DNA repair mechanism that eliminates a wide spectrum of single-strand damages causing local helix-destabilization, for example, pyrimidine dimers the most important DNA damages caused by UV [182]. NER carries out its function in two sub pathways which include global genomic NER (GG-NER or GGR) for localizing damages anywhere in the genome, and transcription coupled NER (TC-NER or TCR) for eliminating transcription-stalling damages and allowing quick resumption of transcription [183]. The difference between these two sub pathways comes down to how they identify DNA lesions [183]. They are the same in damage incision, repair and ligation process. Identification of the lesion leads to elimination of a short single-stranded DNA part that contains the damage. DNA polymerase uses undamaged single-stranded DNA as a template to synthesize a short complementary sequence [184]. Finally, ligation is done by a DNA ligase and NER process. The proteins involved in NER include: XPC and XPA to recognize and verify lesions, XPF and XPG work as 5′- and 3′-exonucleases respectively, polymerase sigma or epsilon, RFC, PCNA which fills in the gap and ligase I or IV that seal RNA [184]. Just like the BER pathway, NER machinery is also a potent target of various polyphenols. For example, chemopreventive activity of green tea polyphenols against photocarcinogenesis was reported to be mediated by NER pathway. The expression levels of major proteins involved in this pathway, including XPA, XPC, RPA1, DDB2, and DDB1, was significantly increased in the skin of mice treated with polyphenols after UVB exposure [185]. In addition, it was revealed that polyphenols repair UV-induced DNA damage in XPA–proficient cells of a healthy person, but not XPA-deficient cells obtained from XPA patients, indicating that a NER mechanism is involved in DNA repair [185]. Black raspberry extract reduced levels of DNA adducts and inhibited mutagenesis relative to the oral leukoplakia cell line treated with dibenzo [a,l]-pyrene (DBP) [186]. This effect is due to increased repair of DNA adducts (NER pathway) and not metabolism of DBP [186]. XPA, ERCC5, and DNL3 have been reported to be targeted by ellagic acid. Additionally, mice fed with this polyphenol showed significantly decreased DNA adducts, indicating that ellagic acid reduces endogenous oxidative DNA damage by mechanisms that may involve increase in NER machinery [187].

4.4.2.3. NEHJ and HR. The main repair mechanism for DSBs is HR repair and NHEJ. HR is a kind of genetic recombination event in which nucleotide sequences are exchanged between two similar or two of the same molecules of DNA. Since it is based on a homologous template, HR occurs only during the S and G2 phases [188]. There are three phases in HR, namely pre-synapsis, synapsis, and post-synapsis. The initial step is processing DNA to a 3′-overhanging tail by a Rad51 filament commonly referred to the pre-synapsis step. The synapsis step consists of homology search and DNA strand invasion catalyzed by core proteins [188]. When the homologous DNA is found, Rad51 mediates DNA strand invasion reaction. Subsequently, DNA synthesis from the 3′-end of the invading strand is done by DNA polymerase η, followed by consecutive ligation by DNA ligase I to produce a four-way junction midway structure known as a Holliday junction [189]. This intermediate recombination is removed by one of three ways: i) dissolution mediated by the BLM-TopIIIα complex, ii) symmetrical split by GEN1/Yen1 or Slx1/Slx4, ii) asymmetric split by the structure specific endonuclease Mus81/Eme1 [189]. Shirode et al. demonstrated that pomegranate extract inhibited breast cancer cell growth by inducing cell cycle arrest in G2/M followed by the induction of apoptosis. It was also shown in DNA microarray analysis that PE downregulated genes associated with mitosis, chromosome organization, RNA processing, DNA replication, and DNA repair, particularly HR pathway. Major genes involved in HR,

Table 2
The role of polyphenols in the modulating of apoptosis in response to DNA damage.

Polyphenol	Target	Concen.	Target gene	DDR evaluation	Major finding	Ref.
Myristicin	Leukaemia K562 cells	250 μM	Caspase-3	Measurement the expression of ERCC1, RAD50, RAD51, ATM, GADD45A, GADD45G	Induced apoptosis via the mitochondrial pathway Down regulated of DDR genes including ERCC1, RAD50, RAD51, ATM, GADD45A, GADD45G	[289]
Punicalagin	PC-3, lncap and BPH-1 cell lines	100 μM	Caspase-3, caspase-8	Comet assay	Exerted anti-proliferative activity in prostate cancer cells via induction of apoptosis and anti-angiogenic effect	[290]
Grape seed proanthocyanidins	JB6 C141 cells	20–80 g/ml	P53, Bax, caspase-3, cytochrome c, Apaf-1, caspase-9	Comet assay	Induced p53-dependent apoptosis	[291]
Resveratrol	T-cell acute lymphoblastic leukemia MOLT-4 cells	30 μM	Bax, bcl2, p53, caspase-3, caspase-7	Comet assay	Enhanced DNA damage Arrested cell cycle arrest at G0/G1 phase Induced mitochondrial membrane Induced depolarization and apoptosis	[292]
Geraniin	Splenocytes,	0.8 μg/ml and 1.6 μg/ml	Bax, Bcl2, p53	Comet assay	Downregulated gamma radiation-induced apoptosis by suppressing DNA damage	[293]
Green tea polyphenol	P53-proficient L0-2 and p53-deficient Hep3B cells	30 μg/ml	Bax/Bak, Bcl2, caspase-3	N/A	Induced apoptosis in p53-independent pathway, related to the translocation of Bax and Bak to mitochondria, released cytochrome c, and activated of caspases	[294]
EGCG	Non-small cell lung cancer cell lines Lung carcinoma-derived cell line, the human colorectal adenocarcinoma cell line mouse-derived lung adenocarcinoma cells	5 – 50	N/A	Measurement of 8-OH-dg	Induced ROS production, oxidative DNA damage, and apoptosis	[295]
Fruit Peel Polyphenolic Extract	Breast Cancer Cells	150 μm	Bax, Bcl2, caspase-7, Bad, PARP Akt, p38 MAPK, and ERK 1/2	Measurement of ATM and histone H2AX	Induced caspase-dependent cell death associated with increased oxidative stress Modulated activity of the Akt, p38 MAPK, and ERk 1/2 pathways Modulated the signaling of ROS mediated DNA damage.	[296]
Chafuroside B	Keratinocytes	0.3 or 1 μm	IL-10, TNFα, PGE2, caspase-3, caspase-7	Evaluation of formation of cyclobutane pyrimidine dimers	Ameliorated UVB-induced DNA damage and generation of photoimmunosuppression Related mediators	[297]
Strawberry polyphenols	Human dermal fibroblasts	50 μm	Pikb, IL-6, IL-1 TNFα, Nrf2, catalase, SOD, HO-1	Apoptosis detection	Reduced cell death and ROS, increased antioxidant defense, lowered inflammatory markers, and improved mitochondrial functionality	[298]
Scutellarin	Prostate cancer cells	0-600 μm	Caspase-3, caspase-9, Bcl-2, Bax, Cdc2, cyclin B1	Comet assay, Measurement of histone H2AX	Suppressed cell proliferation by promoting G2/M arrest and inducing apoptosis Sensitized cancer cells to cisplastin treatment Induced DNA damage	[125]
Quercetin, chlorogenic acid, And (-)-epicatechin, strawberry and plum extract	Human hepatoma cell line	Various concentrations	N/A	DNA fragmentation analysis	Suppressed cell proliferation by promoting G1 arrest and inducing apoptosis	[299]
Chalcones	Human bladder cancer cells	3-5 μm	Cyclin B1, cyclin A, Cdc2, p21, p27 Bcl-2, Bcl-XL, Bax, Bak, caspase-9, caspase-3	N/A	Suppressed cell proliferation by promoting G2/M arrest and inducing mitochondrial apoptosis	[119]
5-Methoxyflavanone	Human colon cancer cell	40 μm	ATM, ATR, Chk2, Chk1, p53, p21, caspase-2, caspase-7, PARP, ERK1/2, MDM2	Measurement of ATM and histone H2AX	Induced cell cycle arrest at the G2/M phase, apoptosis and autophagy Induced DNA damage	[120]
Ferulic acid	Pancreatic β-cells	0.1–1 mm	N/A	Determination of DNA strand breakage	Prevented methylglyoxal-induced protein glycation, DNA damage, and apoptosis in	[300]
Anthocyanins	Promyelocytic leukemia cells	0.05–4.0 nm	P38 MAP kinase, c-Jun, ERK, FAS, caspase-8, caspase-3, BID, Bcl-2, Bax, cytochrome c	Determination of DNA strand breakage	Mediated apoptosis via the p38-fasl and Bid pathway	[301]
Anthocyanin from of Georgia-grown blueberries	Colorectal cancer cell line	50 to 150 μM	Caspase-3	Determination of DNA fragmentation	Decreased GST and quinone reductase Induced apoptosis	[302]

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Table 2 (*continued*)

Polyphenol	Target	Concen.	Target gene	DDR evaluation	Major finding	Ref.
Naringenin,	Male Swiss albino male mice	50 mg/kg	P53, Bax, Bcl-2, NF-κB	Comet assay	Protected against radiation-induced apoptosis Inhibited the NF-kb pathway Decreased DNA damage	[303]
Genistein	Human lymphoma cell lines Raji, Ramos, and Jurkat	7.4–74 μM	PARP, Akt	Comet assay	Inhibited proliferation Induced G2/M arrest Increased apoptosis	[304]
Genistein	Human Lymphoblastoid cells	20.0 μM	N/A	Micronucleus assay	Inhibited proliferation Induced G2/M arrest Increased apoptosis	[305]
Daidzein	BEL-7402, A549, hela, hepg-2, MG-63	100 μm	Bcl-2, Bcl-x, Baid, Bim, caspase-7	Comet assay	Induced apoptosis Caused cell cycle arrest at the G2/M phase Increased DNA damage	[306]
Daidzein	Hepatic cancer cells	200 and 400 μm	PRDX3, APRT, CTP, KRT-9, -10, Bcl-2, Bcl-xl, APAF-1, caspase9, caspase-3	Comet assay	Induced apoptosis Increased DNA damage	[307]
Quercetin and curcumin	HT1080 cells	20–30 μm and 8-60 μm	P53	Measurement of histone H2AX	Increased in DNA damage Induced cell cycle arrest at G1 phase Increased apoptosis	[132]
Quercetin	HL-60 cells HP 100 cells	30 μm	Topoisomerase II	Measurement of 8-oxodg levels	Increased 8-oxodg formation Increased in DNA damage Inhibited of Topoisomerase II activity Increased apoptosis	[308]
Resveratrol	Glioma cells	30 μm	ATM, Chk2, Wee1, pcdk1	Measurement of ATM and histone H2AX	Abrogated the Temozolomide-induced G2 arrest leading to mitotic catastrophe and reinforces the Temozolomide-induced senescence	[72]
Resveratrol	Prostate cancer cells	2.5 And 5 μm	P53, p21cip1, p27kip, Akt, mTOR, AMPK	Measurement of histone H2AX	Enhances the radiation-induced inhibition of clonogenic survival Inhibited radiation-mediated cell cycle arrest and induces cell accumulation at G1-S and sub-G1 phases consistent with apoptosis	[69]
Resveratrol	Osteosarcoma cells	25 and 50 μm	P53, CHK1, ATM, BCL2, BAX	Measurement of histone H2AX	Induced S-phase arrest, DNA damage response and cellular senescence Induced replication and oxidative stresses	[309]
Resveratrol	Human chronic Myelogenous leukemia cells	60 μm	Caspase-3, JNK1/2, ERK1, ERK2, p38, Bim, Bcl-2	Measurement of histone H2AX	Activated p38 and JNK, and blocked the activation of ERK. Induced apoptosis and DNA damage	[310]
Resveratrol	Thyroid cancer cells	100 μm	ERK1, ERK2, p53, p21, c-Fos, c-Jun	DNA fragmentation	Induces apoptosis via a MAPK- and p53-dependent mechanism	[311]
Resveratrol	Mouse skin	50 μm	P38, p53, c-Jun, MAPK, ERK1, ERK2	Comet assay	Suppressed tumors growth by inhibition of activated MAPK and p53 Inhibited cellular proliferation and induced apoptosis	[312]
Resveratrol	Lung cancer	50 μm	Caspase 3, p53, p21, EF1A, PARP,	Measurement of histone H2AX	Induced premature senescence correlated with increased dsbs and ROS Increased apoptosis	[313]
Resveratrol	Hacat Cells	100 and 25 μm	MAPK, p21, p53, Akt, p27, Bcl2, Bax,	Measurement of histone H2AX	Reduced UVB-induced ROS formation Enhanced the detrimental effect of UVB on hacat cell vitality Increased UVB-induced caspase 8, PARP cleavage Induces autophagy and apoptosis	[314]
Resveratrol	Murine prostate cancer cells	50 and 100 μm	Bax, Bcl2	Measurement of histone H2AX	Induced mitochondria-mediated, caspase independent apoptosis Increased DNA damage	[315]
Resveratrol	Pancreatic cancer cell	50 μm	N/A	Measurement of Comet assay	Enhanced growth inhibitory and apoptotic potential	[316]
Resveratrol	Human gastric Cancer cells	50–200 μm	Sirtuin1	Measurement of histone H2AX	Induced apoptosis and DNA damage via ROS, but independent of sirtuin1	[317]

(*continued on next page*)

Table 2 (*continued*)

Polyphenol	Target	Concen.	Target gene	DDR evaluation	Major finding	Ref.
Curcumin	Testicular tissue of male Wistar rats	30 mg/kg	Bcl-2, p53, PCNA, Bax, caspase-3	DNA fragmentation	Induced DNA in correlation with mitochondria dependent apoptosis and failed PCNA related	[318]
Curcumin	Rat liver	80 mg/kg	Caspase-3, and caspase-8	Comet assay Micronucleus test	Prevented the formation of DNA damage Decreased apoptosis	[319]
Curcumin and Ellagic acid	Cervical carcinoma Cells	16 μm	P21, p53, Bax	Comet assay	Induced ROS generation, DNA damage, p53 accumulation and apoptosis	[320]
Curcumin	Diabetic rats liver	1200 mg/kg	Caspase-3, p53, PARP, Bcl-xl, Bad, Bax, Bcl-2, p38, ERK1, ERK2	DNA fragmentation	Protected rat liver from streptozotocin-induced diabetic pathophysiology by counteracting ROS and inhibiting the activation of p53 and MAPK- mediated stress response pathways	[321]
Curcumin	PC12 cells	50 and 100 μm	Caspase-3, caspase-9, Bcl-xl, Bad, Bax, Bcl-2, ATM, ATR, p53	Measurement of histone ATM, ATR, histone H2AX	Suppressed H2O2-induced cytotoxicity Inhibited the loss of mitochondrial membrane potential (Δψm) through Regulation of Bcl-2 family expression, Reversed H2O2-induced apoptotic cell death	[322]
Curcumin	Sprague-Dawley Rats	200 mg/kg	N/A	Measurement of 8-ohdg	Suppressed N-methyl-N-nitrosourea-induced photoreceptor apoptosis Reduced the level of 8-OHdG	[323]
Curcumin	Colon cancer cells	0-50 μm	Caspase-3, Bax, cytochrome c, p53, p21	Comet assay	Induced the production of ROS and Ca^{+2} Decreased the levels of mitochondria membrane potential and induced apoptosis.	[324]
Curcumin	Resting human T cells and leukaemic Jurkat cells	0-50 μm	ATM, Chk2, Chk2, P53, caspase-2, caspase-8, caspase-9, PARP	Measurement of histone H2AX	Induced apoptosis	[325]

such as MRE11, RAD50, NBS1, RAD51, BRCA1, and BRCA2, were significantly downregulated by treatment with pomegranate extract. Resveratrol was also reported to strongly inhibit several genes of HR, DNA replication, and cell cycle in breast cancer cells [190]. Liu et al. by comparing the survival of wild type with isogenic DNA-repair deficient DT40 cell lines demonstrated that HR mutants of Brca1−/− and Brca2−/− cells were more sensitive to resveratrol. The sensitivities of cells were associated with enhanced DNA damage in terms of accumulation of γH2AX foci and number of chromosome aberrations. Therefore, resveratrol-induced DNA damage and repair pathway play critical roles in response to resveratrol-mediated genotoxicity. Various repair genes have been identified, such as APEX, ERCC1, ERCC2, ERCC4, MGMT, OGG1, XPA, XPC, XRCC1, XRCC3, AHR, and CYP1A1. Guarrera et al. [191] showed that a flavonoid-rich diet significantly upregulated XRCC3, as central gene in HR, in healthy male smokers.

In contrast to HR which requires a homologous sequence, in NHEJ the fractured ends are directly ligated without needing homologous template [192]. Some of the essential factors that are consecutively required to DSB sites are used in NHEJ mechanism. The initial step in the NHEJ pathway implicates identification and binding of the Ku70/Ku80 heterodimer (Ku) to the exposed DNA termini of the DSB [192]. Structurally, the three-dimensional structure of Ku70/80 exposes a preformed ring-shaped structure that completely surrounds the DNA duplex [193]. After binding to DNA, the Ku-DNA complex needs the catalytic subunit of DNA-PKcs to produce the DNA-PK holoenzyme with protein kinase activity. The binding of the DNA-PKcs molecules on contrary DSB ends assists synapsis or tethering of the two DNA molecules [193]. In addition, synapsis of DNA-PKcs causes autophosphorylation of DNA-PKcs, making the DNA termini available. In NHEJ, two members of the X family DNA polymerases, Pol μ and Pol λ, are needed for synthesizing missing nucleotides. After processing the DNA termini, DNA ligase IV along with its binding partner, XRCC4, carry out the ligation of the DNA ends [194]. The underlying mechanisms of chemosensitization by curcumin have been demonstrated to be relied on two major DDR pathways: NHEJ and the DNA damage checkpoint [107]. Curcumin suppressed the histone acetylation at DSB sites by inhibiting histone acetyltransferase activity, thereby reducing recruitment of the key NHEJ factor KU70/KU80 to DSB sites. It also inhibited ATR kinase, resulting in impaired activation of ATR-Chk1 signaling necessary for DNA damage checkpoint pathway [107]. Curcumin suppressed two DDR pathways by inhibiting histone acetyl transferases and ATR. In mice exposed to radiation, ferulic acid abrogated γ-radiation induced oxidative stress and DNA damage by up-regulating nuclear translocation of Nrf2 and activation of NHEJ pathway [195]. Ferulic acid pretreatment regulated the nuclear translocation of p53, inhibited ATM activation, expression of GADD45a gene, and activated NHEJ [195].

4.4.3. *Effectors of apoptosis*

Apoptosis is another important DDR effector. With more stringency and accuracy in comparison to cell-cycle arrest or repair, it has the ability to decrease the risk of cell accumulation with compromised genomes [26]. More importantly, apoptosis is a key cell death modality in different pathologic conditions, including tissue damage in cerebrovascular decease, cardiovascular diseases, and cancer, to name a few of these conditions [196]. Induction of apoptosis by various polyphenols has been described in a several numbers of studies as a, particularly in the case of cancer. It has been extensively demonstrated that administered alone, in combination with conventional chemotherapy, radiotherapy, or with other polyphenols, these natural compounds appear active to prevent the incidence and spread of cancer, among which apoptosis play a considerable function. In addition, polyphenols are reported to modulate apoptosis in response to DNA damage in various cancer cells, such as bladder, breast, prostate, colon, leukemia, lung, liver, ovary, glioma and skin cancers Polyphenols regulate extrinsic and

intrinsic pathways of apoptosis by targeting key players of these pathways, including caspases, B-cell lymphoma-2 family protein (Bcl2), as well as inhibitor of apoptosis proteins (IAPs). A comprehensive list of studies about the role of polyphenols in the modulating of apoptosis in response to DNA damage is represented in Table 2.

5. Conclusions

Polyphenols possess antioxidant capability and have been shown to hamper oxidative stress, as well as subsequent cellular damages and inflammation. Following any damage to cellular genomes, DDR and its key players (e.g., DDR sensors, such as MRN complex) are triggered to detect and sense DNA lesions and set an intricate cascade into motion. This is done in order to eliminate deleterious damages. Afterwards, DDR transducers (including serine/threonine kinases, ATM and ATR) are activated to amplify and transmit signals form sensors to mediators. Other key players in response to DNA damage are mediator proteins, which synchronizes the temporal-spatial control of the multiple factors in the DDR. These include promoting their activation, recruiting other components, or regulating their association with damaged DNA. Signal transduction through upstream transducers conveys information about DNA damage to DDR effectors, which then elicit the most appropriate response by either cell cycle arrest, recruitment of DNA repair machinery, or induction of apoptosis. Another important DDR effector with more stringency and accuracy in comparison to cell-cycle, apoptosis, eliminates the risk of cell accumulation with compromised genomes.

Declaration of Competing Interest

None.

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