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Review Article

Targeting the DNA damage response (DDR) of cancer cells with natural compounds derived from *Panax ginseng* and other plants

SeokGyeong Choi [a,1], Minwook Shin [a,1], Woo-Young Kim [a,b,c,*]

[a] College of Pharmacy, Sookmyung Women's University, Seoul, Republic of Korea
[b] Muscle Physiome Research Center, Sookmyung Women's University, Seoul, Republic of Korea
[c] Research Institute of Pharmaceutical Sciences, Sookmyung Women's University, Seoul, Republic of Korea

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ABSTRACT

DNA damage is a driver of cancer formation, leading to the impairment of repair mechanisms in cancer cells and rendering them susceptible to DNA-damaging therapeutic approaches. The concept of "synthetic lethality" in cancer clinics has emerged, particularly with the use of PARP inhibitors and the identification of DNA damage response (DDR) mutation biomarkers, emphasizing the significance of targeting DDR in cancer therapy. Novel approaches aimed at genome maintenance machinery are under development to further enhance the efficacy of cancer treatments. Natural compounds from traditional medicine, renowned for their anti-aging and anticarcinogenic properties, have garnered attention. Ginseng-derived compounds, in particular, exhibit anticarcinogenic effects by suppressing reactive oxygen species (ROS) and protecting cells from DNA damage-induced carcinogenesis. However, the anticancer therapeutic effect of ginseng compounds has also been demonstrated by inducing DNA damage and blocking DDR. This review concentrates on the biphasic effects of ginseng compounds on DNA mutations—both inhibiting mutation accumulation and impairing DNA repair. Additionally, it explores other natural compounds targeting DDR directly, providing potential insights into enhancing cancer therapy efficacy.

1. Introduction

Cancer is a disease caused by genetic changes, and DNA damage is a primary factor contributing to these changes. When DNA damage occurs, it can disrupt the normal regulation of cell growth and division. If not repaired, DNA damage can result in mutations in the genetic code or other regulatory sequences, disrupting the normal functioning of cells. Cells possess intricate DNA repair mechanisms that can fix most types of damage. However, in some cases, DNA repair may be incomplete, or errors may occur, leading to the persistence of DNA damage. Certain types of DNA damage, such as mutations in proto-oncogenes (genes that may cause cancer), tumor suppressor genes, or DNA repair genes, can trigger uncontrolled cell proliferation, facilitate the accumulation of mutations and chromosomal changes, and ultimately lead to the development of cancer.

Notably, DNA damage is common in cells, and cells have evolved mechanisms to repair DNA damage and prevent the development of cancer. However, in certain cases, when DNA damage overwhelms repair mechanisms or if the repair mechanisms themselves become faulty, the risk of carcinogenesis increases. This means that mutations are drivers of cancer development.

Paradoxically, while genomic alterations drive cancer initiation and progression, they also create a vulnerability that can be exploited by DNA-damaging therapies, such as radiation, alkylating agents, and poly-ADP-ribose polymerase (PARP) inhibitors. When exposed to these therapies, cancer cells, whose repair capacity is already compromised due to mutations, may cease dividing and eventually die. Defects in the DNA damage response (DDR) contribute to genomic instability, a hallmark of cancer. However, cancer cells may develop resistance to these treatments during the course of therapy.

Recently, PARP inhibitor-driven "synthetic lethality" in cancer cells harboring *BRCA1* or *BRCA2* mutations suggested that targeting the DDR may sensitize cancer cells that already have defects in the machinery involved in maintaining genomic integrity [1]. In the same context, a novel targeting strategy for these genome maintenance machinery may enhance the effects of many already clinically available

* Corresponding author. College of Pharmacy, Sookmyung Women's University, Seoul 04310, Republic of Korea.
E-mail address: wykim@sookmyung.ac.kr (W.-Y. Kim).
[1] The two authors contributed equally.

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chemotherapeutic agents and irradiation therapies. In that regard, many novel reagents targeting genome maintenance machinery are under development to enhance the efficacy of chemotherapy or radiation therapy.

Many natural compounds derived from traditional medicine, which have been used for hundreds of years in various countries, are believed to be beneficial for preventing aging and carcinogenesis. Numerous studies have reported that these compounds not only possess inherent anti-carcinogenesis properties largely through the modulation of reactive oxygen species (ROS) but also enhance the effects of other therapeutic strategies [2–4]. Among these, compounds from *Panax ginseng* Meyer (*P. ginseng*) have demonstrated anticancer activity by targeting the aforementioned DDR. In this review, we summarize the effects of *P. ginseng*-derived compounds, focusing on their effects on the ROS, DNA damaging and DDR in cells. The biphasic effects of these compounds on DNA mutations—both inhibiting mutation accumulation and inhibiting DNA repair—will be discussed, along with the exploration of other natural compounds targeting the DDR directly.

2. ROS and mutations

2.1. ROS as a cancer inducer and a cancer therapeutic tool

In the eukaryotic cellular system, which is water-based, ROS, including hydroxyl radical (HO•), superoxide radical (O2•), and hydrogen peroxide (H_2O_2), are generated through various cellular metabolic processes and external stimuli. While ROS are produced during normal metabolism, they were initially recognized as harmful to many cellular events, including the maintenance of DNA integrity. However, a contemporary understanding acknowledges that ROS also play a beneficial role in numerous cellular events, as they are essential for modulating crucial signaling pathways.

ROS are primarily produced in mitochondria, peroxisomes, and the endoplasmic reticulum [5] through processes involving the electron transport chain complex, NADPH oxidase, cyclooxygenase, lipoxygenase, and other fundamental metabolic enzymes [6]. Additionally, exogenous stimulation from external sources can induce ROS. Notable examples include therapeutic treatments for cancer involving radiation and various chemotherapeutic agents, such as platinum-based drugs, alkylating agents, and topoisomerase inhibitors. These treatments induce high levels of ROS, which play a critical role in their anticancer effects [7].

ROS damage DNA by forming adducts of bases and breaking phosphodiester bonds. ROS can oxidize adenine and guanine (8-oxoA and 8-oxoG) in DNA [8] or cause single-strand break (SSB), either directly or indirectly. Therefore, induced ROS are a primary driver of cancer cell death during chemotherapy and radiation therapy. However, there is another side to the role of ROS in carcinogenesis. Prolonged exposure to increased ROS leads to the accumulation of mutations in cells, which are believed to be major contributors to cell aging. Moreover, accumulated mutations in oncogenes and tumor suppressor genes drive cells toward cancer development, suggesting that ROS are key players in carcinogenesis. Approximately more than 10,000 oxidative bases are generated or lost in a cell due to ROS every 24 h [9].

The effects of increased ROS levels in precancerous and cancer cells lead to opposite outcomes, and consequently, the use of ROS modulators in treatment may result in beneficial outcomes [7]. ROS also induce modifications in lipids and proteins in toxic ways, contributing to the therapeutic effects of treatments through apoptosis.

In contrast, moderate levels of ROS are also required to control cell proliferation and differentiation [10]. Therefore, cell systems must have fine-tuned mechanisms to eliminate excess ROS. ROS, which are generated in the cell hundreds of thousands of times a day, are removed by a complex scavenging system composed of enzymes such as glutathione peroxidase, glutathione reductase, superoxide dismutase, and others, which convert ROS into stable molecules [5,11]. Additionally, transcription factors such as NRF2 exert antioxidative effects via transcription [12].

Many natural compounds are reported to play diverse antioxidant roles in cells. In the same vein, we may derive benefits from these natural compounds in suppressing carcinogenesis and delaying the aging process induced by ROS. The antioxidant role of *P. ginseng* has been well demonstrated in the literature [13]. Furthermore, numerous studies support the therapeutic potential of *P. ginseng* in cancer [14,15]. The contradictory effects of *P. ginseng* components in cancer in relation to ROS will be discussed later.

3. DNA repair mechanisms targeted by cancer therapeutics

3.1. Repair of base substitutions

The most common types of DNA damage involve single-strand damage, where only one strand of the DNA double helix is affected. This damage can manifest as SSB or chemical modifications of DNA bases [16]. In addition, both endogenous and exogenous cancer therapeutics often induce crosslinking of two DNA strands.

The modified bases in single strands can lead to incorrect base pairing during the replication process or impede the progression of the replication fork. To address these issues, cells employ several efficient repair mechanisms, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and direct reversal. We will briefly review BER and NER, as they are well-known contributors to carcinogenesis and are targets of many chemotherapeutics and natural compounds.

BER is a DNA repair pathway designed to correct base damage resulting from oxidative, alkylation, deamination, and depurination/depyrimidination [17]. The BER pathway is divided into two sub-pathways, ‘short patch’ and ‘long patch’, based on the number of nucleotides in the repair tract.

DNA glycosylases play a pivotal role by recognizing and catalyzing the cleavage of damaged bases. This step removes the damaged base, creating an apurinic or apyrimidinic site (AP site). An AP endonuclease or a DNA AP lyase further processes the repair by creating a nick (SSB) through cleaving the DNA backbone phosphodiester bond. DNA polymerase and ligase collaborate to fill in the gap with the correct nucleotide, using the other strand as a template. In addition to these four proteins, PARP1 recognizes and binds to nick/SSB, becoming activated. It then undergoes poly-ADP-ribosylation (parylation) on itself and neighboring proteins, facilitating the formation of repair complexes. When parylation is inhibited, the BER process is blocked, leading to the accumulation of SSB.

NER is a DNA repair mechanism designed to eliminate various helix-distorting DNA lesions, such as cyclobutane pyrimidine dimers (CPDs) formed upon exposure to UV light irradiation and bulky DNA adducts induced by environmental chemical compounds or cytotoxic drugs [18]. NER consists of two subpathways: global genomic NER (GG-NER) and transcription-coupled NER (TC-NER) [19]. NER excises a 24- to 32-nucleotide long DNA stretch containing the damaged base and patches it using the undamaged strand as a template for repair synthesis. In mammalian GG-NER, the XPC protein complex detects helix distortion and stabilizes the DNA bend [20]. The DNA-dependent ATPase/-helicase TFIIH unwinds the DNA helix and creates a 20-bp open bubble structure [21]. Replication protein A (RPA), XPA and XPG join the preincision complex, and then, a dual incision is made between ERCC1-XPF and XPG [21,22]. Finally, repair synthesis is accomplished by the same proteins involved in replication, polymerase δ or polymerase ε and ligase 1 [23,24].

3.2. Repair of SSB and DSB

As mentioned earlier, SSB can be generated by ROS, other chemicals, and radiation and during normal cellular processes such as replication

and repair. When two neighboring SSB occur, they lead to the formation of DNA double-strand break (DSB). Additionally, if SSB are not promptly repaired, encounters with replication forks during the S phase of the cell cycle can result in DSB. Approximately 50,000 SSB and 25 DSB are generated daily [25,26].

SSB lesions are fixed by SSB repair mediated by multiple protein complexes. Briefly, PARP1 recognizes the SSB site. The scaffold protein XRCC1 is recruited, forming a complex with Lig3α, polymerase β, and polynucleotide kinase 3′-phosphatase. This complex works collaboratively to fill and ligate the broken strand [27].

DSB are highly cytotoxic because they lead to chromosomal instability. There are four known repair pathways for DSB: conventional nonhomologous end joining (cNHEJ), homologous recombination repair (HRR), alternative end joining (alt-EJ), and single-strand annealing (SSA) [28]. The choice of the DSB repair pathway depends primarily on whether DNA end resection occurs [28,29]. Resected DSB can be repaired by HRR, alt-EJ, and SSA. Among them, cNHEJ and HRR are two major DSB repair pathways and are briefly discussed.

3.3. cNHEJ

cNHEJ is a common and rapid pathway for repairing DSB that occur throughout the cell cycle. This pathway does not require end resection but involves small deletions of 1–4 base pairs at noncompatible DSB ends [30]. Despite its mutagenicity, cNHEJ is beneficial for protecting genome integrity from large deletions or translocations of chromosomes [28].

The cNHEJ process is initiated by the binding of the Ku70 and Ku80 heterodimers to DSB ends. The Ku70-Ku80 heterodimer protects DNA ends from unwinding and degradation, simultaneously recruiting other cNHEJ factors, such as DNA-dependent protein kinase catalytic subunit (DNA-PKcs), DNA ligase IV (LIG4), and the associated scaffolding factor XRCC4. This protein complex brings the two ends of the DSB in close proximity, a process known as DNA-end synapsis [31,32]. Artemis nuclease, polymerase μ, and polymerase λ also promote cNHEJ in specific circumstances as accessory factors [33]. The binding of 53BP1 to the DSB site suppresses the end resection required for homologous recombination repair (HRR), directing repair toward the cNHEJ process when HRR is not available.

3.4. HRR

HRR is the second major pathway for DSB repair and is the preferred repair mechanism due to its error-free nature. Unlike cNHEJ, HRR exclusively occurs in the S and G2 phases of the cell cycle when a sister chromatid template is available. The initiation of DNA end resection is facilitated by binding of the MRE11-RAD50-NBS1 (MRN) complex to the DSB site. The initial processing step involves “short-range” resection mediated by MRE11 and CtBP-interacting protein (CtIP). MRE11, functioning as an endo/exonuclease, nicks the strand up to 20 base pairs away from the break site in mammalian cells and extends the nick toward the DNA end [28,34–36]. Further “long-range” resection is carried out by exonuclease 1 (EXO1), Bloom syndrome helicase (BLM), and endonuclease DNA2 [37,38].

Following resection, the 3′ single-strand tails (ssDNA) generated are rapidly stabilized by RPA complex binding. RPA serves to open secondary structures in ssDNA and protects it from pairing with other ssDNAs. Importantly, RPA prevents the loading of the recombinase Rad51 onto ssDNA, inhibiting the formation of a nucleoprotein filament. BRCA2 competes with RPA for ssDNA binding and facilitates the displacement of RPA with Rad51 [39–41]. The Rad51 nucleoprotein filament then invades duplex DNA molecules that have a matching sequence, providing a template for repair polymerization. In this step, the BRCA1-BARD1 complex stimulates invasion and homologous pairing [42]. Once a sufficient number of bases are paired, the non-base-paired strand of the invaded molecule is displaced, forming a displacement loop (D-loop). By utilizing the invaded DNA template, DNA polymerase δ extends the invading strand [29,43].

HRR is the preferred process for cells that encounter DSB, as it does not result in any DNA loss or mutations. However, this process can only be executed when sister chromatid templates exist. Therefore, cells unable to undergo HRR must patch breaks with cNHEJ, which predominantly occurs in G1 but is available throughout the cell cycle. This choice may be less harmful than losing large fragments of chromosomes in subsequent mitosis.

In cases where cells cannot efficiently undergo HRR, such as in *BRCA1*- or *BRCA2*-mutant cells found in some familial breast and ovarian cancer patients, these cells become highly vulnerable to drugs that can induce SSB. PARP inhibitors, for example, are toxic to HRR-defective ovarian and breast cancer cells due to *BRCA1* or *BRCA2* mutations. This concept forms the basis of synthetic lethality in the DDR utilized in cancer therapy.

4. Compounds from *P. ginseng* protect cells against DNA damage

Ginsenoside Rg3 might protect fibroblasts and liver cells from Benzo [*a*]pyrene (BaP)-induced DNA damage through the activation of the phosphatidylinositol 3-kinase/Akt/Nrf2 pathway [44]. It was recently demonstrated that carcinogenesis induced by BaP can be inhibited *in vitro* and *in vivo* by the ginsenoside Rg3 through this mechanism, and this effect can be further enhanced through P-glycoprotein transporter inhibition [45]. They also found that ginsenoside Rg3 reduced BaP-induced cytotoxicity and DNA adduct formation in human lung cells and rescued phase II enzyme expression through the NRF pathway.

The ginsenoside Rh2 demonstrated antioxidant capacity in porcine oocytes against oxidative stress by regulating the expression of SIRT1 (silent information regulator of transcription 1), PGC-1α (peroxisome proliferator-activated γ receptor coactivator 1-α) and the antioxidant gene superoxide dismutase 1 (SOD1), resulting in the enhancement of mitochondrial activity [46]. Although this study did not address DNA mutations directly, it is possible that ginsenoside Rh2 can also reduce ROS-induced DNA damage. Interestingly, multiple studies also have shown that ginsenoside Rh2 actually induces ROS. This will be described later.

Ginsenoside Rg1 inhibited the oxidative stress-induced increase in the p53 and p21 proteins and sustained DNA damage during hematopoietic stem cell senescence [47].

The ginsenoside compound-Mc1 decreased oxidative stress and increased cell viability in the heart muscle cell line, H9c2. *p*-AMPK and SOD2 levels were increased by the ginsenoside compound-Mc1, resulting in a decrease in the production of H_2O_2-mediated ROS [48]. The ginsenoside Rp1 inhibited the expression of DNA damage-related signaling molecules induced by ionizing radiation (IR), interfering with the IR-induced production of nitric oxide (NO) and interleukin (IL)-1β in macrophages [49]. NO, known for its high reactivity, can directly damage DNA [50] or interact with ROS [51].

There are *P. ginseng* derived non-ginsenosides compounds that modulate ROS. Maltol (3-hydroxy-2-methyl-4-pyrone) is a natural organic compound synthesized from maltose and amino acids that accumulates during the heating process to make red ginseng [52]. Maltol also showed antioxidant activity in various *in vivo* and *in vitro* contexts via the NF-κB and Akt pathways [53]. ROS-induced cytotoxicity and DNA fragmentation decreased with the addition of maltol [54].

Ginseng oligopeptides (GOPs) are derived from *P. ginseng* through bioenzymatic digestion possess antioxidative properties. These compounds have been shown to counteract the cellular senescence induced by ROS-mediated DNA damage [55]. Withaferin A (WFA), a bioactive compound found in Indian ginseng, exhibits anti-ROS effects, particularly in mitigating DNA damage in bladder cancer cells [56]. Proteins extracted from wild *P. ginseng* adventitious roots (AREs) can reverse UVA irradiation-induced cell death in NIH-3T3 cells through AKT activity [57].

There are several reports of the direct use of *P. ginseng* extracts. Black ginseng, a type of steam-processed *P. ginseng* extract, displays antioxidant properties by scavenging ROS, maintaining redox status, and activating the antioxidant defense system in liver cells [58]. Korean Red Ginseng (KRG) extract has been shown to suppress ATM-Chk2-p53 dsDNA damage responses by reducing ROS in *H. pylori*-infected gastric epithelial cells [59]. Similar effects were noted with other natural compounds, such as lycopene [60] and α-lipoic acid [61]. *H. pylori*-induced ROS are implicated in stomach carcinogenesis [62], and KRG extract suppresses the activation of NADPH oxidase, a source of ROS, in *H. pylori*-infected cells [63]. Seo et al. [64] demonstrated a positive correlation between the anti-ROS effect and the composition of ginsenoside Rg3, along with a negative correlation between the total ginsenoside content and the amount of DNA damage caused by oxidative stress. Consequently, the extracts obtained from *P. ginseng* roots, which contain various ginsenosides, exhibited both anti-ROS and anti-genotoxic effects.

Direct treatment with *P. ginseng* has been shown to modulate oxidative stress and DNA damage induced by silicon dioxide nanoparticles in rats, which are commonly used in cosmetics and biomedical applications [65].

UVA and UVB rays are also important contributors to DNA damage in humans. UVA primarily induces DNA damage through the formation of CPD [66]. *P. ginseng* proteins (GP), specifically 27 kD and 13 kD, have been demonstrated to alleviate UVA-induced damage to NIH-3T3 fibroblasts [67]. UVB exposure results in various types of DNA damage, including damage to CPDs and 8-hydroxyguanine (8-OHdG), leading to gene mutations [68,69]. Ginsenoside Rg2, a component of *P. ginseng*, has been shown to activate p53 and p-p53, suppressing UVB-induced DNA damage, as quantified by the amount of cyclobutene. Consequently, ginsenoside Rg2 treatment mitigates cell death and autophagy induced by UVB in the breast cancer cell line MCF-7 [68].

5. Compounds from *P. ginseng* exhibit DNA damage effect with the potential therapeutic activity of cancer

Contrary to these anti-ROS effects observed with many ginsenosides, the opposite effect of the same ginsenosides has also been reported. While ginsenoside Rh2 was shown to reduce ROS, as described previously, it increased ROS and induced DNA damage when cells were treated with sunitinib, a VEGFR inhibitor. This effect was evidenced by an increase in chromosomal DNA breaks detected through gH2AX and comet assays, along with the induction of oxidative stress-damaged DNA indicated by elevated levels of 8-OHdG [70]. Ginsenoside Rh2 stimulates the production of mitochondrial ROS, leading to apoptosis in cervical cancer cells by inhibiting the mitochondrial electron transfer chain complex III [71]. In addition to this direct mechanism, ginsenoside Rh2 was found to induce epigenetic changes and transcriptional regulation related to ROS metabolism. It led to histone deacetylation of the NR2F2 promoter, enhancing transcription [72]. NR2F2 overexpression, in turn, causes mitochondrial dysfunction and increased ROS production, contributing to DNA damage [73]. These findings suggest that the ginsenoside Rh2 may induce DNA damage through various pathways, making it a potential therapeutic agent.

Ginsenoside Rg3 plays dual and seemingly paradoxical roles in the DDR. Ginsenoside Rg3 enhances the radiosensitivity of lung cancer A549 and H1299 cells by downregulating the PI3K/AKT signaling pathway [74]. This finding suggests a potential therapeutic role in sensitizing cancer cells to radiation treatment. In another study, ginsenoside Rg3 significantly protected DNA integrity and inhibited carcinogenesis both *in vivo* (a urethane-induced carcinogenesis model) and *in vitro* [75]. This protective effect was attributed to the activation of the VRK1/p53BP1 pathway. VRK1, which is activated by ionizing radiation, phosphorylates p53BP1, forming foci at DNA DSB sites for cNHEJ. Ginsenoside Rg3 arrested the prostate cancer cell [76] through inducing ROS though the mechanism was not clarified. The paradoxical nature of the effects of ginsenoside Rg3 on ROS and DNA, including its protective role against mutagenesis induced by BaP (previously described), suggests that its effects on DNA may be regulated by complex and possibly context-dependent mechanisms. Further research is needed to elucidate the intricate molecular pathways underlying the dual roles of ginsenoside Rh2 and ginsenoside Rg3 in the ROS and DDR. These paradoxical effects may also depend on cellular context (normal/precancer/cancer and active metabolism) and exposure concentration and duration to the ginsenosides.

The ginsenoside compound K was also found to enhance ara-C-induced DNA damage in AML cells in a comet assay [77]. Since ara-C is an antimetabolite drug that blocks DNA polymerase activity, the protective mechanism may not be related to ROS.

6. Ginsenosides directly modulate DNA repair mechanisms or DNA damage machinery

We have presented an overview of both the protective and harmful effects of *P. ginseng* compounds on DNA, with a significant focus on their relation to ROS. Recent research has successfully revealed intricate details regarding the mechanisms of DNA repair. Investigations are currently ongoing to understand the direct effects of *P. ginseng* compounds on the DNA repair mechanism.

In 2018, Zhen and colleagues reported a direct mechanism for enhanced DNA damage related to the DDR mediated by ginsenoside Rg1. Affymetrix cDNA array analysis revealed that ginsenoside Rg1 impaired the HRR [78] of DSB in hepatoblastoma (HB) cells. Notably, ginsenoside Rg1 was found to suppress the expression of CtBP-interacting protein (CtIP), a key factor in DSB repair. CtIP was more highly expressed in tumor HB tissues than in normal tissues [79]. Consequently, the loss of CtIP sensitized HB cells to various DNA-damaging agents, including camptothecin, hydroxyurea, mitomycin C, radiation, and UV rays.

Notably, these diverse agents, each of which induces DNA damage through different mechanisms, exhibited similar sensitization effects when treated with, ginsenoside Rg1. This suggests that the effect of ginsenoside Rg1 may not occur through a common mechanism, such as ROS. Furthermore, *in vivo* results demonstrated that the combination of ginsenoside Rg1 with a PARP inhibitor, a direct DDR targeting agent, efficiently promoted DNA damage and significantly suppressed tumor growth. Collectively, these findings strongly suggest that ginsenoside Rg1 is directly involved in the DNA repair process itself rather than in the induction of DNA damage through processes such as oxidative stress or the production of base adducts.

Mitomycin C, a DNA crosslinking cancer chemotherapeutic agent, has been shown to induce the expression of Rad51, a key molecule in HRR, likely through the ERK pathway [80]. Interestingly, *P. ginseng* extract, even though they consist of mixed compounds, were found to reduce Rad51 expression. This reduction in Rad51 expression was identified as an essential process for combination therapy-induced cell death.

Ginsenoside Rd has a protective effect against mitochondrial DNA (mtDNA) and nuclear DNA damage, potentially increasing the survival of neurons in a rat model of brain ischemia, specifically middle cerebral artery occlusion (MCAO). This protective effect was associated with the upregulation of NEIL1 and NEIL3 expression at both the mRNA and protein levels. NEIL1 and NEIL3 are DNA glycosylases that play a role in initiating BER by cleaving damaged bases caused by ROS [81,82]. This protective effect of ginsenoside Rd may not be limited to neurons suggesting that it has a potential protective effect on normal cells exposed to cancer therapeutic agents.

The Connectivity Map (CMAP) is a powerful chemogenomic tool that serves as a reference database of transcriptome data from cultured human cells treated with various drugs. CMAP enables the repositioning of drugs and identification of novel targets for natural compounds [83] (https://www.broadinstitute.org/scientific-community/software/conn

ectivity-map). Byun et al. recently demonstrated that components of *P. ginseng* exhibit topoisomerase I inhibition effects similar to those of camptothecin and irinotecan, which are widely used cancer therapeutic drugs [84]. The transcriptomic profiles of the *P. ginseng* components matched those of known topoisomerase I inhibitors. Additionally, *P. ginseng* extract displayed topoisomerase inhibitory effects *in vitro* and exhibited synthetic lethality via the suppression of the *WRN* (helicase) gene.

Comprehending the molecular mechanism by which *P. ginseng* provides protection against damage signaling remains challenging. This difficulty is, in part, attributed to the presence of multiple components in *P. ginseng*, each exhibiting various biological activities on multiple targets at different levels. The intricate interplay of these components adds complexity to their contributions to both damage and repair processes.

7. *P. ginseng* compounds lead to epigenetic changes that regulate DNA damage and repair responses in chromatin

The components of *P. ginseng* also play a role in modulating epigenetic changes in DNA and chromatin proteins. This contribution is crucial for transcriptional regulation and repair processes [85].

Epigenetic modifications include methylation of CpG islands in gene promoter regions and posttranslational modifications of histones, such as methylation, acetylation, and phosphorylation [86]. These modifications of chromatin proteins critically regulate DNA repair [87]. Methylation of promoter DNAs generally suppresses gene expression, while histone lysine methylation can either activate or suppress transcription, depending on the position of modified amino acids in histone subunits. The acetylation of histones is correlated with gene expression. The key players in epigenetic gene regulation include DNA methyltransferases (DNMTs), histone methylases, histone demethylases, histone acetyltransferases, and histone deacetylases. These factors are closely linked to chromatin ultrastructure and interact with other transcription regulators and chromatin remodeling factors [88–90]. Chromatin structure and protein interactions are critical determinants of DNA repair processes, and various histone modifiers, as well as ubiquitin ligases, play important roles in DDR [91,92].

P. ginseng extract downregulates the expression of DNMT1, DNMT2, and DNMT3 in colorectal cancer (CRC) cells, leading to increased global hypomethylation of genes, including the global methylation marker LINE1, and other protein-coding genes [93,94]. Although the total extract of *P. ginseng* was used in this study to examine epigenetic regulation, isolated compounds such as ginsenoside Rh2 and ginsenoside Rg3 have also been shown to modulate epigenetic changes. For instance, ginsenoside Rh2 has been demonstrated to increase hypomethylation of LINE1 CpG islands, resulting in the upregulation and downregulation of numerous genes in MCF-7 breast cancer cells [95]. Additionally, ginsenoside Rg1 has been found to repress *Smad7* methylation via miR-152-mediated DNMT1 inhibition, demonstrating that DNMT1-mediated epigenetic changes are induced by *P. ginseng* components [96]. Another study by Zhao et al. revealed that ginsenoside Rg3 downregulated the expression of DNMT1, DNMT3a, and DNMT3b, leading to hypomethylation of the promoters of p53 and hMLH1 with subsequent increased expression [97].

Ginsenoside Rg3 has been found to attenuate radiation-induced DNA-PKcs expression, sensitizing nasopharyngeal carcinoma cells to radiation [98]. As mentioned earlier, DNA-PKcs is a key player in the cNHEJ repair pathway for DSB [99]. In addition to the modulation of transcription largely through the promoter DNA methylation, *P. ginseng* components such as ginsenoside Rg3 have been shown to influence histone codes. For instance, in ovarian cancer cells, ginsenoside Rg3 increased the acetylation of H3 K14/K9 and H4 K12/K5/K16 [97]. Ginsenoside Rh2, on the other hand, increased the acetylation of the promoter of Coup-TFII [72], a factor related to mitochondrial dysfunction and ROS production. Ginsenoside Rh2-induced hypomethylation of the promoter includes KDM5A, an H3K4me3 demethylase. KDM5A plays a crucial role in the epigenetic regulation of DNA repair, collaborating with PARP1 and the ZMYND8-NuRD chromatin remodeler to promote DNA repair [100–102]. These epigenetically regulated transcriptional changes induced by ginsenosides, especially ginsenoside Rh2, may be connected to the DDR.

To facilitate a clear understanding of the established effects of ginsenosides on DNA DDR discussed herein, we have organized them in Table 1 along with their structures and original references.

8. Other natural compounds target DNA damage and repair signaling

In addition to ginsenosides, various natural compounds, such as resveratrol, curcumin, epigallocatechin-3-gallate (EGCG), triptolide, quercetin, berberine, and genistein, have been identified as effective in modulating ROS and DNA repair pathways [103,104]. This diverse array of compounds highlights the potential of using ginsenosides as sensitizing agents for cancer cells, suggesting a broader strategy to enhance the efficacy of cancer treatment.

8.1. Natural compounds that target ROS

Several natural compounds have demonstrated protective effects against ROS generation. For instance, curcumin and resveratrol significantly mitigate ROS production induced by arsenic treatment [105–109]. Specifically, curcumin has been shown to reduce arsenic-induced ROS levels, as evidenced by decreased 8-OHdG levels. In addition to its protective role, curcumin has anticancer effects on human gastric cancer cells (hGCCs), primarily attributed to its pro-oxidative effect at high concentrations, which induces ROS production in cancer cells. This activity is accompanied by an inhibition of proliferation, colony formation, and migration in a dose-dependent manner [110]. Similarly, EGCG offers protection by reducing radical-induced DNA damage in human leukocytes [111], while quercetin prevents oxidant-induced DNA damage in Caco-2 cells by upregulating the mRNA expression of human 8-oxoguanine DNA glycosylase (hOGG 1) [112].

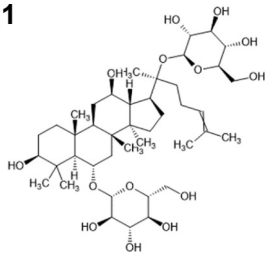
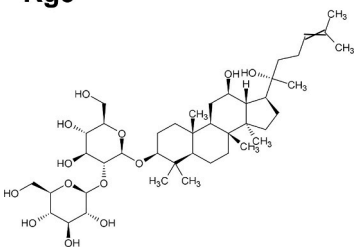
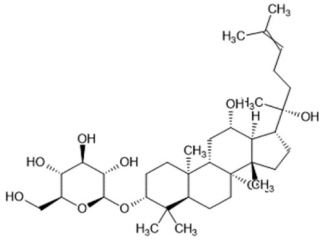
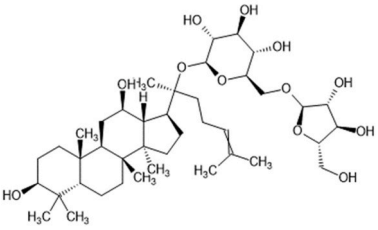
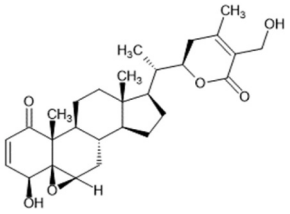
Compounds with antioxidation potential have been extensively studied due to the known anti-aging and health-supportive effects of the plants from which they originate. Therefore, the anti-ROS effects of most of the compounds described herein are supported by numerous investigations. However, some of these studies have reported that these compounds increase ROS levels. For example, genistein enhances ROS-induced oxidative damage upon doxorubicin treatment, resulting in a reduction in the expression of the oxidative DNA repair enzyme apurinic/apyrimidinic endonuclease 1 [113].

8.2. Natural compounds that directly target DNA repair mechanisms

Recent studies have elucidated the important roles of natural compounds in modulating DNA repair mechanisms. In this context, we will focus on several natural compounds that are widely studied as anticancer agents that target DNA repair pathways.

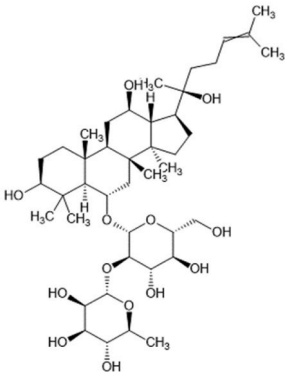
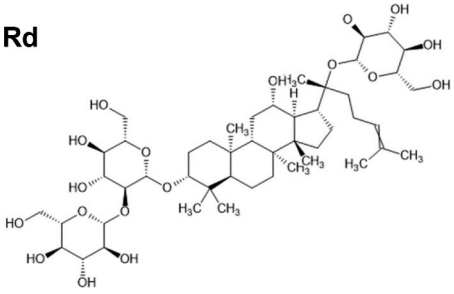
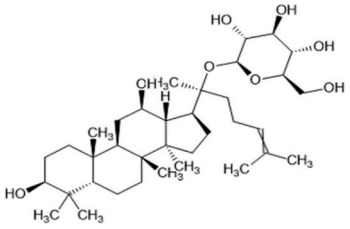
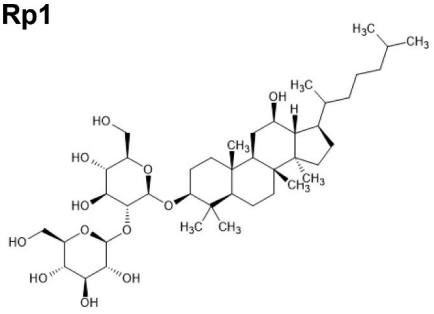
Resveratrol pretreatment has been shown to enhance DNA repair after ionizing irradiation in mouse embryonic stem cells [114]. It stabilizes histone H2AX associated with DNA DSB and effectively reduces replication stress-related DSB in mouse embryonic fibroblasts [115]. Furthermore, resveratrol not only induces DNA damage but also activates repair mechanisms in cancer cells, demonstrating a dual role in modulating the DDR [116]. Resveratrol has been shown to induce DNA damage in head and neck squamous cell carcinoma cells [117]. In combination with pemetrexed, resveratrol increases cytotoxicity in the non-small cell lung cancer (NSCLC) cell lines H520 and H1975 by reducing the expression of ERCC1, a key component of the NER pathway [118]. Resveratrol inhibited the proliferation and increased the death of NSCLC cells induced by etoposide through the downregulation of the

Table 1
The *P. ginseng* driven compounds and the effect on DNA damaging and DNA damage responses (DDR). ↑, induction or increase; ↓, suppression or decrease.

Protection of DNA	Compounds	Targeting DDR
↓ oxidative stress-induced increase of the p53 and p21 [47]	**Rg1** 	Directly impair the homologous recombination (HRR) [78] ↓ decrease CtIP (HRR protein) [79] ↑ DNMT1 inhibition [96]
↓ BaP induced DNA damage through Nrf2 pathway [44] ↓ BaP-induced DNA adduct formation [44] protected DNA integrity by activation of the VRK1/P53BP1 pathway [75]	**Rg3** 	↑ radiosensitivity by PI3K/AKT [74] ↓ DNMT1, DNMT3a, DNMT3b/↑ p53 and hMLH1 [97] ↓ DNA-PK expression [98] ↑ acetylation of H3 K14/K9 and H4 K12/K5/K16 [97]
↑ SIRT1, PGC-1α. and SOD1 [46] ↑ hypomethylation of the promoter of KDM5A, to promote DNA repair [100–102]	**Rh2** 	↑ ROS and DNA damage with sunitinib [70] ↑ ROS by inhibiting the electron transfer chain complex [71] ↑ acetylation of the promoter of Coup-TFII [72] ↑ NR2F2/mitochondrial dysfunction/ROS [72,73] ↑ hypomethylation of LINE1 CpG islands [95]
↓ROS, ↑ *p*-AMPK and SOD2 levels [48]	**Compound-Mc1** 	
↑ anti ROS proteins (NFE2L2, CAT, SOD1, TXN, GSR, NQO1, HMOX1) [56]	**Withaferin A** 	↑ cleavage of PARP [56]

(*continued on next page*)

Table 1 (*continued*)

Protection of DNA	Compounds	Targeting DDR
↓ UVB-induced DNA damage ↓ activation of p53 [68]	**Rg2** 	
↑ Protect DNA damage ↑ NEIL1 and NEIL3 [81,82]	**Rd** 	
	Compound K 	↑ Enhance ara-C-induced DNA damages [77]
Interfering with the IR-induced production of nitric oxide (NO) and interleukin (IL)-1β [50]	**Rp1** 	
↓ ROS [58] ↓ ATM-Chk-2-p53 DDR by reducing ROS [59] ↓ activation of NADPH oxidase [63] ↓ AKT activity [57] ↓ UVA-induced damage [67]	*P. ginseng* extracts/extracted proteins	↓ DNA repair by decreasing RAD51 [80] Topoisomerase I inhibition via the suppression of the *WRN* (helicase) [84] ↓ Expression of DNMT1, DNMT2, and DNMT3 [93,94]

XRCC1 protein, which is involved in BER [119]. Resveratrol treatment has been show to delay the repair of radiation-induced DSB that lead to apoptosis in prostate cancer cells [120]. When combined with capsaicin, resveratrol reduced BER and increased genotoxicity after radiation in colon cancer cells [121]. The long patch BER was reduced by resveratrol in cigarette smoke condensate-treated breast epithelial cells through the upregulation of p21 and the BER-related protein Fen-1 [122]. Resveratrol augmented the antiproliferative effect of cisplatin and etoposide by preventing the repair of DSB through the inhibition of *RAD51* expression [123,124].

Curcumin, another prominent compound, prevents DNA damage and augments DNA repair in a UVB-induced carcinogenesis model through the upregulation of p53 and p21/CIP1, demonstrating its potential in skin cancer prevention and treatment [125]. In combination with a PARP inhibitor, curcumin enhances the inhibition of BER and increases DNA damage in oral cancer cells [126]. Moreover, curcumin exerts a

radiosensitizing effect on human colon cancer HT-29 cells both *in vitro* and *in vivo* by upregulating the NER genes CCNH and XRCC5 and downregulating LIG4 and PNKP, which mediate DSB repairs [127]. Curcumin also abrogates XRCC1 upregulation by cisplatin treatment in NSCLC cells by downregulating p38 MAPK [128]. Moreover, it sensitizes lymphoma cells to treatment with various DNA-damaging chemotherapy agents by reducing *RAD51* expression and consequently HRR [129]. Curcumin suppresses DDR pathways by inhibiting histone acetyltransferase, reducing BRCA1 expression, and inhibiting ataxia telangiectasia and Rad3-related protein (ATR) kinase, resulting in DSB accumulation [130,131]. Additionally, curcumin inhibits the Fanconi anemia (FA)/BRCA pathway of DNA cross-link damage repair [132,133] and sensitizes resistant cells. In contrast, curcumin induces DNA damage and cytotoxicity by increasing the levels of O^6-methylguanine-DNA methyltransferase (MGMT), BRCA1, and the mediator of DNA damage checkpoint 1 in HeLa cells [134].

EGCG inhibits MGMT expression at both the mRNA and protein levels only in glioblastoma cells but not in nonneoplastic gill cells, thereby increasing the DDR [135]. This is because MGMT reverts DNA lesion O^6-methylguanine back to guanine, playing a crucial role in genome integrity. Additionally, EGCG is a potent inhibitor of ERCC1, reducing DNA repair in the cisplatin-treated human NSCLC cell lines H1299 and H460 [136].

Triptolide covalently binds to ERCC3, thereby inhibiting NER and exhibiting antitumor activity [137]. It sensitizes TNBC to cisplatin by downregulating the expression of repair machinery, including *PARP1, XRCC*, and *RAD51* [138]. Low levels of triptolide inhibit NER by reducing CHK1 phosphorylation and inducing ATM phosphorylation in lung cancer cells treated with cisplatin [139]. Additionally, triptolide increases oxaliplatin-induced apoptotic cell death by inhibiting NER pathway components [140]. Triptolide induces DNA DSB in B-cell lymphoma cells by increasing the expression of Rad51 and phospho-histone H2AX levels [141]. It also enhances the effect of the topoisomerase II inhibitor doxorubicin by downregulating the expression of ATM, a key initiator of DSB [142] Triptolide has been shown to reduce *ATM*, *ATR*, *BRCA1*, *TP53*, *DNA-PK*, and *MGMT* mRNA expression [143,144].

Berberine sensitizes breast cancer cells by inhibiting XRCC1 in combination with cisplatin, camptothecin, and methyl methane sulfonate [145]. Regardless of p53 status, berberine induces DNA damage [146] and reduces Rad51 levels, inhibiting HRR activity to enhance PARP1 inhibitor efficacy [147,148].

Quercetin activates the NRF2/Keap 1 pathway, reducing DNA damage in a 1,2-dimethylhydrazine-induced colorectal cancer model [149]. On the other hand, genistein inhibits UV-induced DNA damage and the expression of proliferating cell nuclear antigen (PCNA) and CPD [150], indicating its protective effects on carcinogenesis. Quercetin also sensitizes cells to radiation-induced DNA damage through a decrease in RAD51 induced by ER stress [151,152].

Genistein binds to DNA-PKcs, inhibiting DNA-PKcs phosphorylation or decreasing the expression of Rad51 and Ku70, consequently inhibiting cNHEJ repair and/or HRR repair pathways [153,154].

9. Conclusions

P. ginseng has been utilized for human health for centuries in Asian countries. Recent advancements in analytical technology and molecular biology tools have enabled the exploration of the molecular mechanisms of compounds derived from *P. ginseng* in human health. Recent progress in cancer therapy, particularly that focused on the DDR and synthetic lethality, highlights the potential importance of *P. ginseng*-derived compounds in DDR targeting.

Despite the well-established biological effects of many ginsenosides, particularly in terms of antioxidant activity, the specific targets and molecular mechanisms involved in DDR remain unclear. However, research on the impact of other natural compounds on DNA repair mechanisms is growing extensively, suggesting that the anticancer effects of *P. ginseng*-derived compounds may also involve the modulation of DDR. Elucidating the potential mechanisms that suppress DDR could provide a solid rationale for the coadministration of *P. ginseng* with DNA-damaging anticancer treatments widely used in clinical settings. To gain deeper insights, more intensive studies utilizing well-defined molecular and chemogenomic approaches are warranted, paving the way for the potential therapeutic and supplementary use of *P. ginseng* for cancer patients.

Declaration of competing interest

The authors declare no conflict of interest.

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