

Prevention of Chromium-Induced Radiation-Chemical Oncogenesis, Including in Offspring, in an Experimental Model: A Systematic Review

Marat Iztleuov^{a, g} , Yerbolat Iztleuov^b , Talgar Abilov^c , Gulmira Iztleuova^d ,
Elyanora Kydyrbayeva^e , Nauryzbay Imanbayev^f 

Abstract

Radiation and chemical-induced cancer are of increasing concern as the various activities of humans continuously elevate the levels of radiation and toxic chemicals in the environment. The prevention of this incidence using alternative medicines-phytopreparations, therefore, becomes pertinent as conventional approaches tend to produce various unwanted side effects. To achieve this, there is a need to understand the various mechanisms of action through which phytopreparations exhibit their protective effects. This systematic review, therefore, aims to explore the mechanism of action of various phytopreparations in the prevention of induced radiation and chemical (chromium) cancer. A systematic review approach following the stipulated guidelines by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to identify research papers published between 2015 and 2025. Four databases, namely Europe PubMed Central (PMC), PubMed, Springer Open, and Wiley Online Library were used to search for related open access papers. A total of 621 research papers were reviewed for suitability to the review objective; however, only five papers met the inclusion criteria, and an additional two papers were sourced from ResearchGate. Thus, a total of seven papers were finally included in the analysis. This review highlights the mechanisms of action of various phytopreparations in the prevention of radiation and chromium-induced cancer. The major

mechanisms of phytopreparations' action in the prevention of induced radiation and chromium oncogenesis majorly involve regulating pro and anti-inflammatory cytokines, improving cell-to-cell communication, and preventing damage to DNA structure.

Keywords: Hexavalent chromium; Gamma-irradiation; Induced oncogenesis; Prevention; Phytopreparations

Introduction

Radiation and chemicals are agents that have been recognized to cause apparent and dangerous alterations in the germ line of higher plants and animals [1]. This effect is on the increase due to various human activities that are continuously altering the natural ecological systems at an extraordinary rate [2]. Nowadays, environmental pollution is directly related to various changes in human health and directly impacts social status. Epidemiological research and analysis have revealed a daily increase in harm to human health as a consequence of damage to the ecological sphere. Swift urban development and industrialized societies particularly compromise air quality, an assessment can be made by considering the accumulated levels of air pollutants [3].

Ionizing and non-ionizing forms of radiation exists. Non-ionizing radiations have low photon energy which makes them harmless, examples include radio waves, microwaves; however, ionizing radiation (including X-rays, gamma rays, alpha-particles, beta-particles, etc.) carries high photon energy, which is required to break tightly bound electrons from atoms in living cells, thereby creating ions that damage the genetic materials of the cell [4]. Ultraviolet radiation (UVR), although non-ionizing, can be detrimental to cells, having been classified as both a mutagen and a nonspecific damaging agent with tumor initiating and tumor promoting properties [5]. The negative impacts of UVR on the skin have been extensively explored, particularly its association with skin cancers including most common human malignancy, such as basal cell and squamous cell carcinomas, cutaneous melanomas, among others [6, 7].

Ionizing radiation, although a rare but potentially dangerous pollutant, occurs in the environment at low levels as a natural

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^aDepartment of Natural Sciences, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan

^bDepartment of Radiology, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan

^cFaculty of General Medicine, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan

^dDepartment of Phthisiology and Dermatovenereology, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan

^eDepartment of Obstetrics and Gynecology, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan

^fDepartment of Oncology, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan

^gCorresponding Author: Marat Iztleuov, Department of Natural Sciences, NJSC "Marat Ospanov West Kazakhstan Medical University", Aktobe, Kazakhstan. Email: izmarat@mail.ru

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event (such as cosmic and terrestrial radiation) and usually does no harm to living things. However, some specific human tasks, such as the testing of weapons and unprecedented events at nuclear power plants, may release ionizing radiation beyond safety limits. This type of radiation may destroy organic molecules such as DNA and result in malfunctions in cell activities, consequently leading to cellular and organismal death. Radioactive contamination can destroy DNA and other biological molecules [8, 9]. Anthropogenic sources of radioactive contamination are evident in the event at Chernobyl in 1986 in the nuclear power plants, which resulted in long-term radioactive pollution [2]. A consequence of radiation from X-rays and gamma rays is the indirect destruction of biomolecules after synthesizing reactive oxygen species (ROSs), particularly superoxide and hydroxide radicals, from intracellular radiolysis. This can have numerous consequences, such as the oxidation of biomolecules and initiation of diverse intracellular signaling pathways [10], and radiation exposure can elevate the incidence of cancer [11].

The plausible unwanted health impacts resulting from exposure to chromium (Cr) necessitated the Environmental Protection Agency (EPA) to establish a threshold contaminant level of 0.1 mg/L total Cr in potable water. Cr (VI) is mostly present in occupational environments due to industrial activities involving leather processing, smelting, welding, and plating of metals [12]. It is also in automobile exhaust and tobacco products, including traditional and electronic cigarettes and hookahs [12, 13]. An estimated 66% of current or past hazardous waste sites on the National Priorities List also contain Cr. Systemic poisoning associated with Cr has been reported in the respiratory, pulmonary, gastrointestinal, dermal and renal systems [12]. The International Agency for Research on Cancer has identified metallic Cr and Cr (III) compounds as group 3 human carcinogens; specific Cr alloys are categorized as group 2B, while hexavalent Cr compounds are classed as group 1 human carcinogens. Cr (IV) is a potent and highly cytotoxic mutagen. DNA mutilation was taught to be the main mechanism of Cr genotoxicity and carcinogenicity; it has however been established that dichromate ions also cause methylation in DNA molecules and gene silencing, suggesting that epigenetic mechanisms may also be connected with these events. Most of the cellular destruction induced by Cr arises from the production of ROS [14].

Cancer is a major cause of death in childhood in the developed nations of the world. An elevated incidence of blood cancer, as well as defects at birth, has been documented in the offspring of fathers who experienced exposure to radiation from nuclear plants and from various diagnostic procedures involving irradiation [15]. Parent exposure - that is, exposure of sex cells to radiation and chemicals - elevates the occurrence of tumors and abnormalities in the child, and gamete cell transformations that cause cancer are transferrable to the next generations [1]. This phenomenon is often referred to as transgenerational carcinogenesis, which is simply the transfer of cancer risk to the untreated offspring of parents exposed to oncogenes before mating [16].

Mutation is a multiple-stage event that involves entry, distribution, biological transformation, and discharge of the genotoxicant from the body, as well as their invasion of cells and cell nuclei, direct or indirect relation of the genotoxicant and/or its

metabolites with DNA molecules, and consequently damage to the DNA. The various mechanisms of radiation and chemical (Cr)-induced oncogenesis is discussed in Table 1 [4, 17-39].

One basic medical philosophy states that "prevention is better than cure". This ancient principle remains relevant with modern approaches to chemoprophylaxis of numerous diseases utilizing antimutagens (amidst other medications) to annihilate the destructive effects of environmental and endogenous genotoxicants on human health [40]. Cancer prevention takes place across the complete disease scope, starting with the primary up to the tertiary prevention and includes multiple schemes, such as molecular prevention, which involves the use of natural or man-made agents that disrupt the primary drivers, principal derangements, or the scope in which these agents function and in which the derangements take place before the penetration of the basement membrane. In essence, molecular prevention includes chemopreventive agents (such as conventional drugs, micronutrients, etc.), vaccines and therapeutic interventions in individuals at elevated risk of cancer due to microbial or some underlying diseases, as all these eventually operate at the molecular level, and possess the tendency to minimize precancer or cancer incidence and death [41]. Chemoprevention is a plausible scheme used to control cancer by halting and impeding its progression. It is one of the most demanding fields of cancer research and is focused on various interferences, including biological, nutritional, and pharmacological aspects [42]. It appraises using biological or synthetic substances to suppress oncogenesis before invading non-tumor cells. It involves primary, secondary and tertiary approaches. The application of dietary phytochemicals is an active approach to primary and secondary chemoprevention [43, 44].

Medicinal plants filled with antioxidants protect cells from harm, thus preventing and controlling cancer and other ailments [45]. The anti-cancer properties of plants are linked to some major bioactive constituents: alkaloids, tannins, flavonoids, phenols, steroids, terpenoids, and saponins [46]. These phytochemicals have both antioxidant and pro-oxidant properties, thereby annealing oxidative DNA damage following mutation in DNA caused by exposure to carcinogenic agents [47-49]. Also, dietary phytochemicals have been observed to trigger many signaling pathways simultaneously, thus reducing apoptosis, blocking cellular proliferation and invasion and stimulating immune system functionality [50-53]. It is, however, still important to further understand the mechanism of action of these vital agents in order to better harness their numerous benefits. One study [54] concluded that there is a need to understand the underlying mechanism of action of the radio-protective agent-Tulsi (a medicinal plant native to Southeast Asia); another study [55] also concluded that an understanding of the mechanisms of action of the traditional Chinese medicine (TCM) is important, and this knowledge is essential to develop new anti-radiation medicines.

Research aim and question

This review aims to evaluate the mechanisms of action of various phytopreparations in the prevention of radiation- and chemically (Cr)-induced oncogenesis, with a particular focus

Table 1. Mechanism of Radiation and Chromium-Induced Oncogenesis

Mechanism	Developmental process
Mutations in DNA	IR can cause all forms of mutations [17]. Mutation in DNA occurs following alterations in the nucleotide sequence that make up DNA strand, which can result from environmental changes such as chemicals or UV rays and random mistakes in DNA replication [18, 19]. UV and IR induce a qualitatively similar spectrum of DNA lesions, including base alterations, base loss, inter- and intra-strand crosslinks, DNA-protein cross links, regions of denaturation, alkali-labile sites, single-strand breaks and double-strand breaks in the deoxyribose phosphodiester backbone [20], as well as clustered DNA lesions [21]. UVA and UVB radiations lead to the excitation of endogenous sensitizing molecules which produce singlet oxygen and oxidative radicals in the presence of oxygen that results in DNA damage. UVC radiation results in direct excitation and subsequent alteration of the purine and pyrimidine rings [20, 22-24]. IR mostly targets DNA [25]. Direct exposure to this form of radiation results in DNA lesion including single- and double-strand breaks [25, 26]. Indirect exposure to IR splits water molecules near DNA, creating hydrogen and hydroxyl free radicals; which can be converted to ROS, OH, H ₂ O ₂ , etc. [4, 27, 28]; the hydroxyl free radical may react with nearby DNA, producing single-strand DNA breaks, which may spontaneously be converted into a double-strand break. Radiation-induced double-strand breaks is considered the most lethal form of DNA damage [26, 29]. The processing and repair of DSBs can result in mutations, as well as chromosome rearrangements, consequently leading to apoptosis or cancer [30]. Exposure to Cr (IV)-containing compounds has also been reported to produce DNA strand breaks, as well as chromosomal abnormalities and genomic instability which is associated with the development of human lung cancer [31, 32].
Epigenetic modifications resulting from non-mutations-based changes in gene expressions	DNA methylation, modification in histones and ncRNAs are all incidents in the development of radiation induced cancer.
DNA methylation	DNA methylation, which is the covalent addition of methyl groups to the DNA fosters gene regulation as such hypermethylation of genomic DNA is linked to gene silencing, while hypomethylation of the DNA is linked to chromosomal instability [33, 34], and a reduction in DNA methylation levels caused by IR results in an increase in DNA strand breaks and enhanced recombination activity [35]. Therefore, the loss of DNA methylation in specific regions of the eukaryotic genome (such as in the non-coding repetitive elements: transposable elements) may result in genomic instability which is considered a primary hallmark of a host of cancers [33, 34].
Histone modification	Histones, structural proteins that control the dynamism of chromatin, thus making gene regulation at all stages of development in higher organisms achievable [36], are made up of several amino acid residues, which when modified affect the structure of chromatin, consequently, alter transcriptional responses [37], as well as all processes that require access to the DNA [38]. Histone modification occurs mainly by acetylation and methylation [39]; changes in histone acetylation levels have been attributed to the occurrence of some tumors via the downregulation of some tumor suppressor genes, and overexpression of the enzymes involved in histone methylation has been shown to spur the progression of various oncogenes [29].
ncRNA	ncRNAs play important roles in disease development including cancers and IR-induced damage. This is because they are involved in the regulation of cellular processes and cellular stress response [29]. Several studies have provided evidence that ncRNAs play an important role in regulating cancer metabolic reprogramming (abnormal metabolism of glucose, amino acids and lipids found in cancerous cells and tissues); this altered metabolic networks mediated by ncRNAs promote carcinogenesis by controlling the expression of metabolic enzymes and transporter proteins via dysregulation in various metabolic signaling pathways [25].

IR: ionizing radiation; ncRNA: non-coding RNAs; DSBs: DNA double-strand breaks; Cr: chromium; H₂O₂: hydrogen peroxide; OH: hydroxyl radical; ROS: reactive oxygen species; UVB: ultraviolet B radiation; UVA: ultraviolet B radiation; UVC: ultraviolet C radiation.

on the mechanisms underlying the protective effects of phyto-preparations against radiation- and Cr-induced cancer.

Methods

Description of method

A systematic literature review was conducted using four major databases to identify research papers relevant to the review theme.

Data sources

The databases used for the search included Europe PubMed Central (PMC), PubMed, Springer Open, and Wiley Online Library.

Data selection

The following keywords were used to retrieve articles relevant to the review topic: “phytochemical preparations for radiation-

and chemical-induced cancer prevention”, “phytochemical preparations for radiation cancer”, and “prevention of induced chromium-radiation oncogenesis”. The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data objectivity

Only open-access research articles published between 2015 and 2025 were considered. Inclusion criteria encompassed studies focusing on radiation-induced oncogenesis, chemoprevention, and experimental models involving animals or *in vitro* (using cell lines) systems. Studies were excluded if they did not involve animal models, *in vitro* experiments, or did not address radiation- or Cr-induced oncogenesis. The database search was conducted on March 1, 2025.

The initial search in the Wiley Online Library yielded 2,579 results, including journal articles, books, and conference papers. Springer Open returned 61 results, Europe PMC yielded 227 results, and PubMed yielded 22 results. In the second stage of the review, filters were applied to include studies published between 2015 and 2025 from open-access journals. This refinement yielded 545 results from Wiley Online Library, 50 from Springer Open, 12 from Europe PMC, and 14 from PubMed. The third stage of filtering involved the removal of duplicates and an assessment of titles and abstracts to determine relevance to the research theme. This process resulted in five relevant papers from Wiley Online Library, zero from Springer Open, eight from Europe PMC, and four from PubMed. A final selection was made based on the predefined inclusion and exclusion criteria, resulting in a total of five eligible papers: three from Wiley Online Library, one from PubMed, and one from Europe PMC (Fig. 1).

Results

The findings from the reviewed research articles (Table 2 [56-62]) highlight several mechanisms of action through which phytopreparations derived from medicinal plants exert protective effects against radiation- and Cr-induced oncogenesis. These phytopreparations were shown to upregulate anti-inflammatory cytokines while inhibiting pro-inflammatory cytokines, thereby reducing inflammation and preventing cellular injury. Furthermore, the phytopreparations enhanced cell viability and metabolic activity by modulating oxidative stress markers and ROSs, which improved intercellular communication and minimized oxidative damage, ultimately preventing apoptosis.

In addition, these compounds promoted DNA repair processes, preventing permanent genetic damage and thereby contributing to genomic stability. The primary mechanisms by which phytopreparations prevent cancer include: 1) modulation of pro- and anti-inflammatory cytokine expression; 2) enhancement of cell viability through improved intercellular communication; 3) preservation of DNA integrity, which supports gene stability. These mechanisms are illustrated and dis-

cussed in detail based on the research studies identified during the systematic review (Fig. 2).

Discussion

Regulation of pro- and anti-inflammatory cytokines

Pro-inflammatory cytokines, mostly interleukin-1 (IL-1) family, IL-6, and tumor necrosis factor alpha (TNF- α), are crucial factors in generating chronic inflammation. This act is made possible via the stimulation of pro-tumorigenic or anti-tumorigenic functions, which depends on the cancer type, tumor microenvironment (TME), and other associated factors. Following the interplay between IL-6 and its receptor, a number of signaling pathways are activated. This interplay stimulates signal transducer and activates some transcription factors followed closely by the transcription of target genes, resulting in inflammation, metastasis and so on [63]. Based on the milieu of events that occur during inflammation, the synthesis of IL-6 by immune cells is commonly caused by infections and tissue injuries. In addition, TNF- α is an inflammatory cytokine that takes part in the control of numerous signaling processes by binding to TNF- α R-1 and TNF- α R-2. The cytokine stimulates the growth of tumor through several mechanisms including enhancing epithelial-to-mesenchymal transition (EMT), boosting the cell differentiation rate and intensifying the rate of angiogenesis amidst other functions [64-67]. TNF- α exhibits pro-tumorigenic activity by promoting angiogenesis, cell proliferation, migration, and the survival of tumor cells. It is a well-recognized inflammatory mediator involved in both malignant and non-malignant conditions [63]. In a study by Dumlulu et al [56], elevated levels of the cytokines IL-6 and TNF- α were observed in the first-generation offspring of rats exposed to gamma irradiation, as well as those exposed to both gamma irradiation and hexavalent Cr, with more pronounced cytokine levels in the latter group. However, normalized cytokine values were recorded in the offspring of rats that received burdock root oil treatment prior to exposure to either gamma irradiation alone or in combination with Cr (VI). Notably, the levels of IL-6 and TNF- α were significantly lower in the offspring of gamma-irradiated rats, suggesting that burdock root oil effectively suppressed cytokine production in the treated groups.

A similar finding was reported by Lyer et al [57], who observed elevated TNF- α levels in rats exposed to gamma irradiation. However, pretreatment with umbelliferone prior to irradiation significantly reduced TNF- α levels, bringing them close to those observed in the control (non-irradiated) groups.

In contrast to the pro-inflammatory activity of IL-6 and TNF- α , IL-10 is a potent anti-inflammatory cytokine that plays a crucial role in attenuating the host immune response to pathogens, thereby minimizing tissue damage and maintaining homeostasis [68, 69]. High levels of IL-10 signaling can interfere with the synthesis of pro-inflammatory cytokines by directly targeting immune effector cells [57]. IL-10 is typically produced later in the inflammatory cascade, following the early release of pro-inflammatory cytokines. Its localized synthesis at the site of inflammation helps establish a balance between

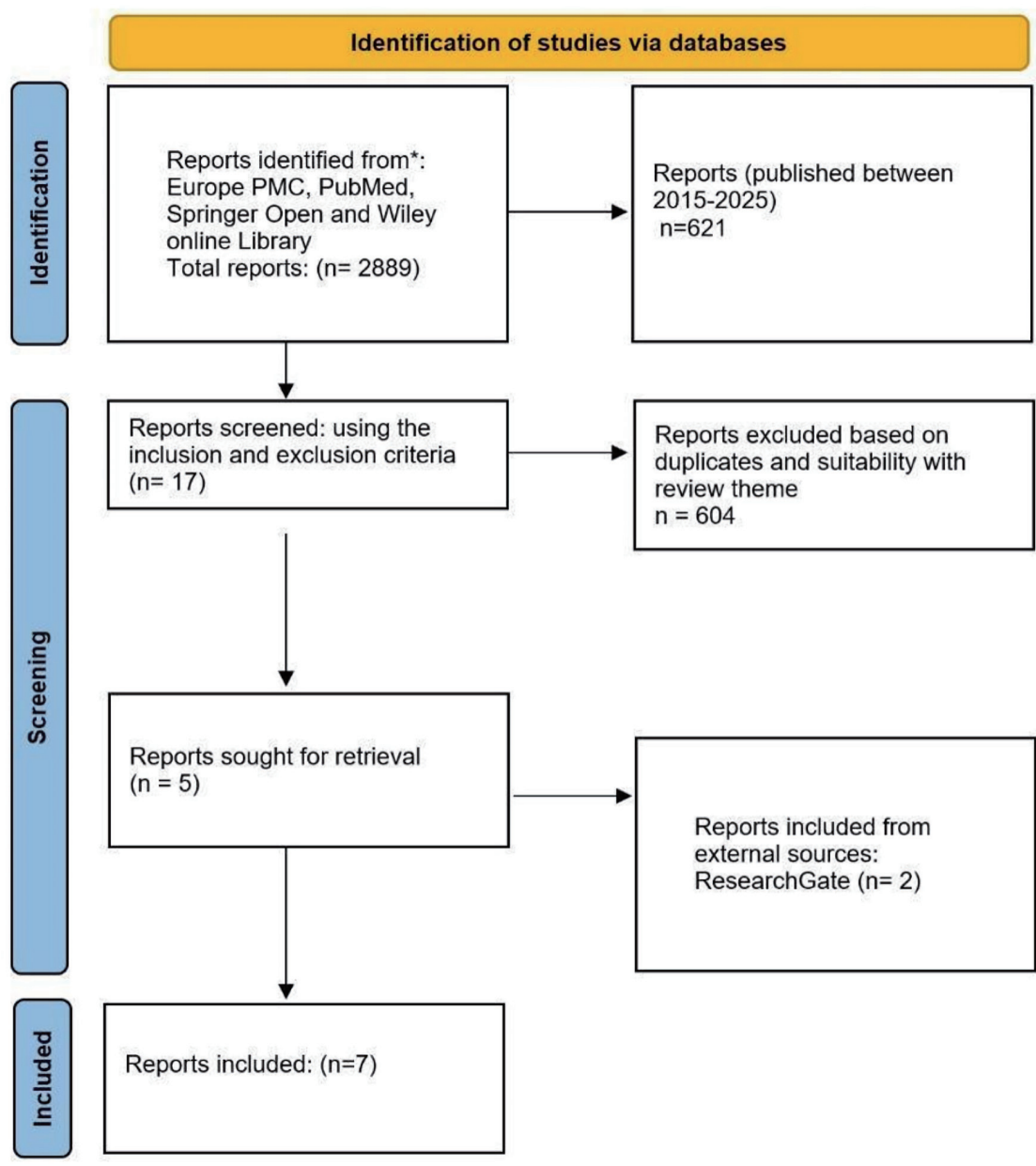


Figure 1. Flow chart for the systematic literature review on the prevention of radiation- and chemical-induced oncogenesis. Source: authors' development in accordance with PRISMA 2020 recommendations. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROS: reactive oxygen species.

effective pathogen clearance and the prevention of excessive immune-mediated damage, ultimately supporting the restoration of normal tissue integrity [69].

The anti-inflammatory activity of IL-10 on gamma-irradiated as well as gamma-irradiated and Cr (IV)-exposed rats was demonstrated by Dumlu et al [56]. IL-10 levels in offsprings of rats, which were administered burdock oil before exposure to gamma irradiation and Cr (IV), were similar to those of the control levels (levels of offsprings of rats not exposed to gamma irradiation as well as gamma irradiation and Cr (IV)). There was significant reduction in the IL-6 and TNF- α val-

ues. Thus, phytopreparation can help regulate pro- and anti-inflammatory cytokines, eliminating the cascade of events that results in inflammation, which is necessary for tumorigenesis, thereby eliminating the incidence of induced cancer and transgenerational oncogenesis.

Efficient and increased cell to cell communication

Cell-to-cell communication is a crucial activity that remarkably determines an organism's homeostasis, growth, and dis-

Table 2. Overview of the Included Research Articles

Reference	Type of exposure	Phytopreparation	Summary of paper
[56]	Gamma-radiation and chromium (IV)	Burdock root oil	Adult male and female rats were exposed to gamma irradiation, hexavalent chromium, and a combination of the two treatments. Prior to exposure, the subjects were treated with burdock root oil. Afterwards the male and female subjects were cross-breed (1:1) to obtain first-generation offspring which later served as the major participants of the research. A positive control group containing similar subjects without exposure to either treatment and two negative controls; subjects exposed to gamma radiation only and those exposed to gamma radiation and chromium (IV) were also set up. The genotoxicity of exposure to offspring was studied using samples from the bone marrow cells, chromosomal aberration was observed to be pronounced in the offspring exposed to both gamma irradiation and chromium (IV) than in either of these agents alone, and it was also observed that the offspring of parents who received treatment prior to exposure to both agents had significant improvements in chromosome integrity, while those treated with burdock root oil and received exposure to either form of the agent had chromosome integrity similar to the positive control group. A 16% decrease in the MDA levels was observed in the group exposed to both agents which was comparable to the levels of MDA observed in the positive control group. Cytokine profile analysis revealed a 43% and 40% increase in the pro-inflammatory cytokines, IL-6 and TNF- α respectively while the level of anti-inflammatory cytokines decreased by 21% compared to the positive control, a strong indication of an imbalance in pro- and anti-inflammatory cytokines. However, offspring from parents that received treatment prior to exposure had IL-10 levels similar to that of the positive control and reduced values of pro-inflammatory cytokines. The study highlighted the anti-oxidative and anti-genotoxic effect of burdock root oil on genotoxicants transferred from parents to offspring.
[57]	Gamma radiation	Umbelliferon (7-hydroxycoumarin)	To determine the impact of umbelliferon on radiation-induced cardiac damages, male rats were exposed to 12 Gy of gamma irradiation and treated with umbelliferon (25, 50, 100 kg/mg body weight per day) prior to exposure. A negative control without treatment with umbelliferon received the same dose of gamma irradiation, while two positive controls included subjects that received physiological saline alone and umbelliferon. Biochemical parameters including TAC and TOS, as well as TNF- α , TXB2 were evaluated using samples collected from heart tissues. In the group exposed to radiation without treatment, the TOS levels increased by approximately 23% and the TAC reduced by 34%, indicative of oxidative imbalance in the heart tissue. This was, however, not observed in the group treated with umbelliferone prior to exposure. It was further observed that the group treated with 100 kg/mg umbelliferone had TOS and TAC values comparable to the positive control group that received physiological saline. This same group was observed to have reduced levels of inflammatory activity as determined by measuring the TNF- α values. Compared to other groups, the value of TXB2 in the irradiated group was significantly elevated, which was indicative of vascular injury; however, the value of TXB2 in the treated group was similar with that of the positive control group, which received physiological saline. Histological examination showed significant damage in the irradiated group, which was not observed in the group that received treatment before exposure to radiation.
[58]	UVB	Acetone extract of green <i>A. linearis</i>	Human epidermal keratinocytes (HaCaT) and melanoma (SKMEL-1) cells were exposed to UVB radiation. Prior to exposure, the cells were cultured in Roswell Park Memorial Institute medium and treated for 4 and 24 h with various concentrations (0, 10, IC ₅₀ and 100 μ mL) of <i>A. linearis</i> . It was discovered that the cytotoxic effect of UVB on cells were both time- and dose-dependent, with the treated cells showing more viability even at low concentration of treatment dosage than the UVB-exposed cells without treatment, indicating the protective activity of the phytopreparation. Further, cell viability was examined using ATP bioluminescence assay, lowest concentration of all treatment significantly increased ATP levels in the HaCaT cells after 4 h of exposure to UVB. A similar observation was reported in the SKMEL-1 cells, which was comparable to that of the control. Caspase 3 activity (indicative of apoptosis) was also reduced by the lowest concentration of the phytopreparation. The cytoprotective activity of <i>A. linearis</i> was associated with the presence of linearitin, aspalathin and nothofagin in this phytopreparation, with linearitin having more pronounced effect than the other compounds.

Table 2. Overview of the Included Research Articles - (continued)

Reference	Type of exposure	Phyto-preparation	Summary of paper
[59]	X-rays	Ferulic acid (FA)	Human lens epithelial cells were exposed to 4 Gy of X-ray. Prior to exposure, the cells were pretreated with FA for 2 h, the positive controls were exposed to sham radiation while negative control were exposed to radiation without any treatment; and all samples were incubated for 72 h. Afterwards, cells were observed under the phase contrast microscope. In negative control, the cells were swollen and disorderly arranged, which was not the case with the pretreated sample as cell morphology was significantly improved. Apoptosis induced by exposure to radiation was analyzed by flow cytometry; it was observed that FA-pretreated cells were resistant to apoptosis in a dose-dependent manner. Further, proteins involved in apoptotic process were quantified; the expression of the Bcl-2 protein (which regulates apoptosis) was significantly increased, while those of the cleaved/caspase-3 (fosters apoptosis) were downregulated. ROS and MDA values were also significantly reduced in the pretreated cells. The molecular mechanism of the antioxidant prowess of the phyto-preparation was assessed by examining the impact of the phyto-preparation on the Nrf2 (genes concerned with the oxidative defense in the eye lens) signaling pathway and its downstream genes. A significant increase in the nuclear Nrf2 and decrease in cytosolic Nrf2 were observed, indicating the efficacy of this agent to stimulate specific pathways capable of releasing products that annihilate oxidative stress induced by irradiation on the lens cells.
[60]	UVB	CTE	Adult male HR-1 hairless mice were exposed to UVB irradiation for 12-week period, thrice weekly, treatment with CTE was administered simultaneously daily (five times a week). A positive control group and a negative control group were also set up. H&E staining revealed CTE's protective effect on the treated cells against UVB-induced epidermal alterations and increased collagen fiber abundance were observed following Masson's trichrome staining. Continuous UVB exposure for 12 weeks resulted in elevation in the levels of MMP associated with UVB-induced skin damage in the skin tissues of mice exposed to irradiation without treatment. CTE administration effectively reduced the levels of MMP, and this effect was attributed to the notable increase in the phosphorylation levels of MAPK signaling pathway, which modulated the expression of MMP. The protective effect of this phyto-preparation on UVB-induced skin photoaging was associated with the presence of acteoside, isoacteoside, among other compounds (martyoside, and isomartyoside) present in this agent.
[61]	UVB	Ursolic acid (UA)	Human skin dermal fibroblast cells were exposed to UVB of 40 mJ/cm ² for 30 min, with the test group comprising cells treated with 10, 20 and 40 μM UA as well as cells prior to irradiated. A negative control and a positive control group were also set up. Fluorescence microscopy shows the presence of dense staining, indicative of pronounced levels of intracellular ROS in the cells exposed to UVB without treatment, which was not the case with either of the positive control and the cells pretreated with 20 μM UA, suggesting the ROS scavenging capacity of this agent; the same concentration of UA also showed maximum protection against UVB-induced oxidative lipid peroxidation compared to other concentrations. Cells pretreated with 20 μM without exposure to UVB showed no damage to DNA, increased ROS or TNF-α and NF-κB (concerned with cytokine production) levels, which were comparable with cells neither pretreated nor exposed to radiation sources.
[62]	Radiation/chemo-therapy for 6 - 7 weeks	Curcumin mouth wash	Adult cancer patients who had undergone radiotherapy and with signs of oral mucositis were grouped into a test and a control group. The control group received chlorhexidine mouth wash, and the test group was treated with curcumin mouthwash each, 3 times daily. Both the standard mouthwash and curcumin were administered for 20 days. The patients were exposed to 65 - 70 Gy of radiation and subsequent treatment with chemotherapy. Erythema and ulceration were recorded using the NRS, E, U and WHO Oral Mucositis Assessment Scale (OMAS). A statistically significant result was reported between the baseline score and the second follow-up score for all scales between the study and control group, indicating the efficacy of curcumin and with no reports on adverse effects in the group that treated with curcumin mouthwash.

A. linearis: *Aspalathus linearis*; *C. trichotomum*: *Clerodendrum trichotomum*; CTE: *C. trichotomum* extract; ATP: adenosine triphosphate; H&E: hematoxylin and eosin; ATP: adenosine triphosphate; E: erythema score; FA: ferulic acid; IL: interleukin; MDA: malonic dialdehyde; MMP: matrix metalloproteinase; NF-κB: nuclear factor kappa; NRS: numerical rating scale; ROS: reactive oxygen species; SKMEL-1: skin melanoma cell line 1; TAC: total antioxidant capacity; TNF-α: tumor necrosis factor alpha; TOS: total oxidative status; TXB2: thromboxane B2; U: ulceration score; UVB: ultraviolet B radiation; MAPK: mitogen-activated protein kinase; WHO: World Health Organization.

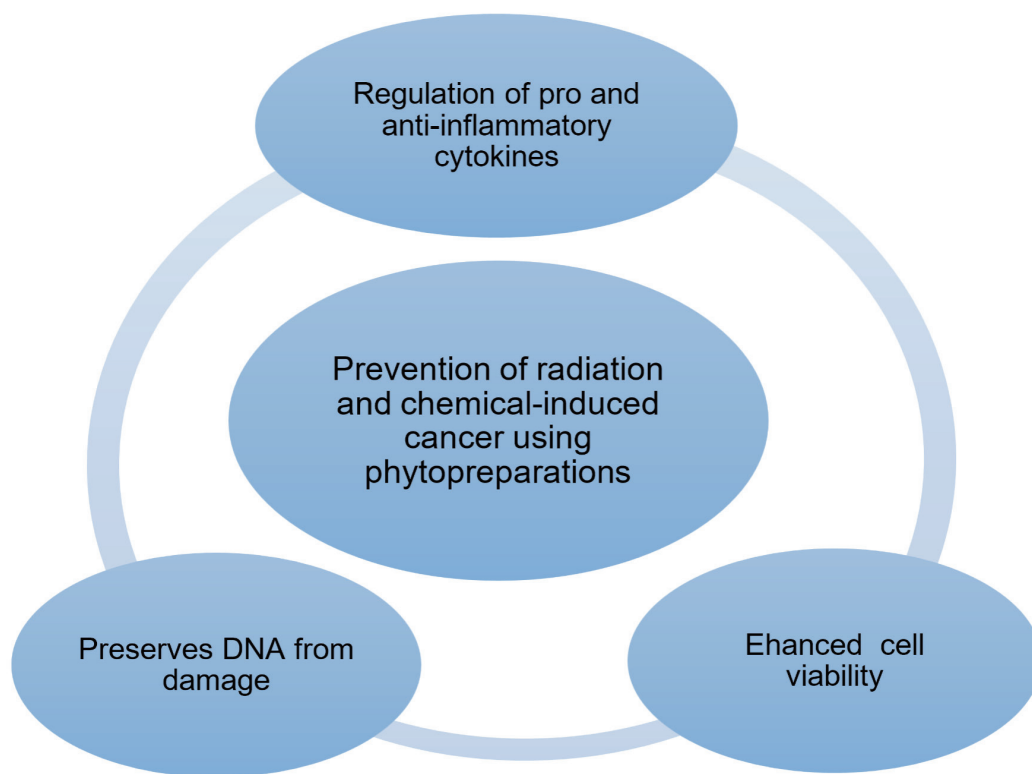


Figure 2. Mechanism for the prevention of radiation-induced oncogenesis using phytopreparations. Source: authors' development.

ease processes. This occurs through direct contact or via the activation of specific cell signaling pathways at a distance using ligand-receptor interactions, which represents a principal means of cell communication and is intricately connected with numerous disease processes and tissue degenerative activities [70]. Cell communication has a foundational role in permitting cancer cells to coopt and regulate stromal and immune cells. The effective communication between the tumor cells and the surrounding cells aids angiogenesis, immune escape, EMT, generation of a pre-metastatic niche, metastases and multi-drug resistance [71].

Adenosine triphosphate (ATP) hydrolysis supplies the energy required to fuel numerous and important activities in cells: intracellular signaling, DNA replication, RNA synthesis, active transport, and signal transduction, among others [72]. ATP acts as a signaling molecule for apt responses to various cytotoxic agents and performs a crucial role in mediating the radiation stress-induced responses that function to control or repair the deleterious impacts of gamma irradiation on the body [73]. ATP serves as a homeostatic messenger and mediator in cell-to-cell communication [74] and also participates in the activities that result in all types of cell death. During the late phase of apoptosis, ATP levels reduce substantially, majorly due to the loss of mitochondrial function and utilization by ATP-dependent proteases [75-77]. In a study by Chen et al [58], the levels of ATP in HaCaT cells (keratinocytes) and skin melanoma cell line 1 (SKMEL-1, melanocytes) exposed to ultraviolet B radiation (UVB) were significantly lower than in the control and treatment

groups. It was further reported that ATP levels in HaCaT cells treated with linearthin, aspalathin and nothofagin from *Aspalathus linearis* (*A. linearis*) prior to UVB exposure were significantly higher than in the unexposed cells. Also, the extracts from *A. linearis* were tested for their anti-apoptotic potential via the activation of caspases 3/7. It was observed that the phytopreparation reduced caspase activation in the UVB-exposed cells. The reduction in apoptotic effects was contingent on the levels of cell damage by UVB exposure, as cells unexposed to irradiation appeared to have a dose-dependent elevation in caspase activity and, consequently, apoptotic cell death. This implies that the phytopreparation enhanced cell viability, thus preventing apoptosis. It was further confirmed that the phytopreparation was not cytotoxic to the cells at low concentrations. In another study by Kim et al [59], the preventive effect of ferulic acid (FA), a phenolic compound present in large amounts in most plants, was investigated. It was reported that human lens epithelial cell (HLEC) line (FHL124) exposed to X-ray and without FA treatment were swollen and showed distorted morphology. However, treatment with FA prior to exposure to irradiation improved cell morphology.

Although the morphology of the treated cells was not identical to that of the control group (cells not exposed to X-rays), the preservation of structural integrity suggests a protective effect of FA, which prevented the complete loss of form in the X-ray-exposed cells. To further assess whether FA protected cells against X-ray-induced apoptosis, flow cytometry was employed to quantify the rate of cell death. A substantial

increase in apoptosis was observed in HLECs following exposure to 4 Gy of X-ray radiation compared with the control group. However, HLECs pretreated with folic acid exhibited dose-dependent resistance to X-ray-induced apoptosis.

In a related study, Perillo et al [60] investigated the effects of *Clerodendrum trichotomum* extract on human epidermal keratinocytes (HEKa) prior to UVB exposure. The extract demonstrated a protective effect by inhibiting UVB-induced cellular alterations. Treated epidermal cells also exhibited increased hydration and enhanced abundance and density of collagen fibers. In addition, mouse skin cells pretreated with the same extract prior to UVB exposure showed significantly reduced levels of biomarkers associated with photoaging. The authors concluded that the extract modulated signaling pathways responsible for the expression of these biomarkers.

Furthermore, moderate increases in ROS contribute to numerous pathological conditions, including tumor initiation and progression. In tumor cells, ROS synthesis is elevated due to increased metabolic activity, genetic mutations, and localized hypoxia. Through interactions with lipids, ROS can promote oxidative stress via a feedback loop initiated by fatty acid peroxidation, which alters the lipid bilayer of cell membranes and leads to the generation of free radicals. This process is harmful to cells. Additionally, ROS interactions with proteins can affect multiple signaling pathways involved in the regulation of cell proliferation and apoptosis [78].

Excessive ROS can be neutralized by elevated levels of antioxidants. Several studies have reported the ability of various phytopreparations to produce a wide range of antioxidants, which have been shown to prevent oxidative stress in cells, thereby reducing cellular damage and inhibiting apoptosis. In a study conducted by Patil et al [61], human dermal fibroblast (HDF) cells exposed to UVB radiation exhibited a significant increase in intracellular ROS generation. However, pretreatment of HDFs with ursolic acid prior to UVB exposure resulted in a reduction in ROS levels, suggesting that the polyphenolic compounds present in ursolic acid were effective in eliminating intracellular ROS generated by UVB-induced oxidative stress.

A similar observation was reported by Chen et al [58], who demonstrated the protective effect of FA in reducing ROS and malondialdehyde (MDA), a lipid peroxidation product, in HKECs exposed to UVB radiation. In a pilot clinical study by Sanders et al [62], a curcumin-based mouthrinse was used to treat radiotherapy-induced oral mucositis in patients. The results showed that curcumin alleviated ulceration caused by radiotherapy, indicating the potential of this phytopreparation to promote oral epithelial cell repair.

Other studies have also demonstrated the efficacy of various phytopreparations in suppressing oxidative stress, enhancing antioxidant levels, and preventing apoptosis in cells exposed to different types of radiation [56, 57].

Preservation of DNA structure and gene stability

The three-dimensional structure of chromosomes plays a crucial role in the regulation of gene expression and also influ-

ences the repair of radiation-induced DNA damage. Genomic aberrations that disrupt chromosomal spatial domains can lead to various pathological conditions, including cancer [79]. Ionizing radiation directly affects DNA structure by inducing strand breaks, particularly double-strand breaks [80]. Mutations in genes and their associated signaling pathways are key factors that determine cell apoptosis, proliferation, survival, and differentiation [70].

The effects of most notable antimutagens depend on their ability to prevent major DNA lesions. These effects generally begin after mutations have occurred, either through the interception and binding of reactive genotoxic molecules by dismutagens or by regulating the synthesis of genotoxic metabolites through the limitation of genotoxicant bioavailability [40]. The antimutagenic effect of burdock root oil was demonstrated by Dumlu et al [56], offspring of adult rats exposed to gamma irradiation and hexavalent Cr exhibited pronounced mutagenic effects, as evidenced by chromosomal aberrations in the bone marrow. However, when the parent rats received burdock root oil prior to exposure to the mutagenic agents (gamma irradiation and Cr), their offspring showed significant improvements in chromosomal structure. Offspring from parents exposed to gamma irradiation alone, who received treatment prior to exposure, exhibited no chromosomal anomalies, with chromosomal aberration values remaining within the control range.

Similarly, Patil et al [61] reported that no DNA damage was observed in HDF cells treated with 20 μ M ursolic acid prior to UVB exposure. All tested concentrations of ursolic acid significantly reduced DNA damage, as indicated by the levels of intact DNA. The World Health Organization has supported and reinforced the integration, recognition, and use of traditional, complementary, and integrative medicines (TCIMs) in national health systems at all levels, including primary health care, specialized care, and hospital care [81].

The discovery and production of safe and potent molecular preventive agents is a promising prospect for cancer prevention [40]. Many researchers are now working on developing new cancer treatment methods, but radiotherapy is currently one of the most powerful and preferred methods of cancer treatment. Unfortunately, although the number of patients treated with this method is increasing by the day, the side effects of the method have not been reduced [57]. Now, the world has focused on natural medicines, and the demand for plant-based medicines is rising. Utilizing novel drug delivery systems with phytoconstituents can result in improved bioavailability, enhanced solubility and permeability, thus minimizing the dose and side effects [82]. An overview of the major phytoconstituents with the mechanism by which they exert their anti-cancer activity is discussed in Table 3 [51, 82, 83, 87-95].

Limitation of the Study

This review utilized research papers with open access and only four databases, and as such the number of research papers included in the study was relatively small. Papers where phytopreparations were used in combination with nanoparticles were not included in this study, limiting the breadth of the study.

Table 3. Major Phytoconstituents With Anti-Cancer Properties and Their Mechanism of Activity

Phyto-chemicals	Mechanism of anti-cancer activity
Flavo-noids and phenolic compounds	The flavonoid structure’s numerous hydroxy groups, combined with a highly conjugated electron system, allow them to act as a free radical scavenger via hydrogen atom or electron-donating activities. They can also inhibit the formation of ROS and act as pro-oxidative compounds [82, 83]. phenolic compounds also exert their preventive role though cell cycle arrest, apoptosis, and most importantly, scavenging free radicals responsible for carcinogenesis and its progression [51, 84-86].
Alkaloids	Alkaloids are a group of ring structure nitrogen containing organic compounds with a wide range of anti-cancer activity [87]. These compounds take part in cancer inhibition via prevention of enzyme topoisomerase activity which is involved in DNA imitation, inducing apoptosis and expression of p53 gene [88-90]. Further, some groups (indole, pyrrole, isoquinoline, etc.) of alkaloids have been reported to exhibit cytotoxic activities against various cancer cell lines by inducing autophagy, necroptosis and apoptosis under the influence of various proteins involved in the apoptotic pathway [91].
Tannins	Inhibition of proliferation of cancerous cells by downregulating the expression of anti-inflammatory enzymes, anti-apoptotic proteins and regulation of specific pathways responsible for tumor cell migration as well as induction of cell cycle arrest [92].
Steroids	Inhibition of tumor growth and stimulation of apoptosis in affected cells by beta-sitosterol. Elevation of antioxidant enzyme activity thereby annihilating oxidative stress damage caused by ROS [93].
Terpenoids	Elevation of cytotoxic activity in tumor cells thereby promoting apoptosis via the stimulation of specific enzymes and pathways [94].
Saponins	Stimulation of pro-inflammatory proteins and pro-survival genes, which in turn leads to activation of cell-cycle proteins, metalloproteinase and apoptotic proteins that regulate cell proliferation and metastasis [95].

ROS: reactive oxygen species.

Conclusions

Cancer prevention has become pertinent considering the adverse effects of radiotherapy and chemotherapy, the rate of industrialization and levels of various environmental pollutants, as well as various economic activities that predispose humans to carcinogenic agents, especially radiation and chemicals (Cr). Phytopreparations from medicinal plants could be a vital key to cancer prevention, particularly those that are radiation and chemical (Cr) induced. It is worthy of note that no observed adverse effect of the phytopreparations on cells were reported by most of the papers included in this systematic review; however, one paper reported toxicity of the phytopreparation to the skin cells (melanocytes and keratinocytes) at the highest concentration experimented but the degree of toxicity and related damage to cell was not reported. Interestingly, the same paper also reported pronounced cytoprotective activity of the phytopreparation at the lowest concentration experimented. More research still needs to be conducted to understand the molecular mechanisms underlying the activity of phytopreparations with particular attention on the role of this agent in genome stability and DNA integrity.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

All authors made an equal and significant contribution to the preparation of the article. Marat Iztleuov, Yerbolat Iztleuov, Talgar Abilov, Gulmira Iztleuova, Elyanora Kydyrbayeva, and Nauryzbay Imanbayev participated in the conceptual development of the research, collection and analysis of data, drafting of the manuscript, and critical scientific revision. All authors have read and approved the final version of the manuscript for publication and agree to be accountable for its content.

Data Availability

The authors confirm that the data supporting the findings of this study are included within the article.

Abbreviations

ATP: adenosine triphosphate; CAT: catalase activity; Cr (VI): hexavalent chromium; E: erythema score; EMT: epithelial-

to-mesenchymal transition; FA: ferulic acid; HDF: human dermal fibroblast; H&E: hematoxylin and eosin; HEKa: human epidermal keratinocytes; HKEC: human keratinocyte cells; HLEC: human lens epithelial cells; H₂O₂: hydrogen peroxide; IL: interleukin; MAPK: mitogen-activated protein kinase; MDA: malonic dialdehyde; MMP: matrix metallo-proteinase; NF-κB: nuclear factor kappa; NRS: numerical rating scale; OH: hydroxyl radical; PMC: PubMed Central; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROS: reactive oxygen species; SH group: sulfhydryl; SKMEL-1: skin melanoma cell line 1; TAC: total antioxidant capacity; TCIM: traditional, complementary and integrative medicine; TCM: traditional Chinese medicine; TME: tumor microenvironment; TNF-α: tumor necrosis factor alpha; TOS: total oxidative status; TXB2: thromboxane B2; U: ulceration score; UVB: ultraviolet B radiation; WHO: World Health Organization

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