International Journal of Biomedicine 13(3) (2023) 17-30
http://dx.doi.org/10.21103/Article13(3)_RA2

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Radiosensitization: Studies and Modern Approaches to Cellular Radiosensitivity

Juan C. Alamilla-Presuel*

The University of Málaga, Málaga, Spain

Abstract

Even though radiation therapy has achieved great success, there is still an unsolved task of increasing radiation damage to tumor tissue and reducing side effects on healthy tissues. There is a wide variety of obstacles that reduce the efficiency of radiotherapy. Mechanisms of radioresistance involve tumor-specific oncogenic signalling pathways, tumor metabolism and proliferation, tumor microenvironment/hypoxia, and genomics. Radiosensitizers are promising agents that enhance injury to tumor tissue by accelerating DNA damage. Several strategies have been used recently to develop highly effective radiosensitizers with low toxicity. In this review, we considered the use of radiosensitizers, including small molecules and nanomaterials, in various malignant tumors and the problems and prospects for their clinical use in cancer therapy.(**International Journal of Biomedicine. 2023;13(3):17-30.**)

Keywords: ionizing radiation • radiosensitizer • cellular radiosensitivity • tumor tissue • DNA damage

For citation: Alamilla-Presuel JC. Radiosensitization: Studies and Modern Approaches to Cellular Radiosensitivity. International Journal of Biomedicine. 2023;13(3):17-30. doi:10.21103/Article13(3)_RA2

Abbreviations

DSBs, double-strand breaks; **EC**, esophageal cancer; **EAC**, esophageal adenocarcinoma; **ESCC**, esophageal squamous cell carcinoma; **HCC**, hepatocellular carcinoma; **HDAC**, histone deacetylase; **HER2**, human epidermal growth factor receptor 2; **HNSCC**, head and neck squamous cell carcinoma; **IR** ionizing radiation; **KRAS**, Kirsten rat sarcoma viral oncogene homologue; **LC**, lung cancer; **PAR**, poly(ADP-ribose); **PARP**, PAR polymerase; **PCa**, prostate cancer; **RR**, ribonucleotide reductase; **ROS**, reactive oxygen species; **SCC**, squamous cell carcinoma; **SCLC**, small cell lung cancer.

Introduction

Radiation therapy is one of the most common forms of cancer treatment. Ionizing radiation (IR) takes effect by indirect or direct action. In direct action, radiation damages molecules such as proteins, lipids, and, particularly, DNA, resulting in the ending of cell division and proliferation as well as necrosis or apoptosis. The indirect action destroys the molecules through free radicals, principally by ROS, which are derived from the radiolysis of water (Image 1).[1] There is a wide variety of obstacles that reduce the efficiency of radiotherapy. Hypoxia is one of the main ones. For most tumors, a significant proportion of tumor cells are exposed to hypoxic conditions and, consequently, are prone to radioresistance.[2] The dependency of cellular responses to IR on the oxygen level has been recognized for almost a century.[3,4] IR causes DNA damage either by direct ionization or indirectly by DNA interaction of radicals formed by ionization of water surrounding DNA, resulting in DNA single- or double-strand breaks.[5] The probability of permanent IR-induced DNA damage is higher in the presence of oxygen than in its absence. In the presence of oxygen, ROS are formed, which increase the overall concentration of DNA-damaging agents. Numerous studies are focusing on elucidating the underlying mechanisms of hypoxia-induced radioresistance and developing strategies

***Correspondence:** Juan C. Alamilla-Presuel. Department of Radiology and Physical Medicine. Medical Faculty. The University of Málaga, Málaga, Spain E-mail: alamillajc@uma.es*

for radiosensitization. Several studies have demonstrated that acute hypoxia increases cell survival and autophagy, selecting for cancer cells with stem cell characteristics, and making them resistant to radiotherapy.[6-8] To limit hypoxia-induced radioresistance, several strategies are exploited, such as increasing oxygen availability by enhancing blood flow, mimicking oxygen, and targeting hypoxic tumor cells.[9]

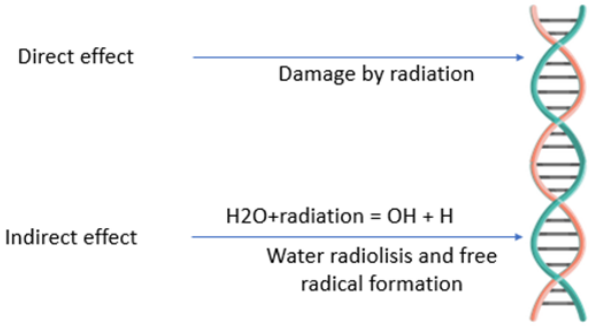

Image 1. *Radiation damage to DNA.*

Improving radio response with radiosensitizers is a promising approach in radiotherapy. Radiosensitizers are promising agents that enhance injury to tumor tissue in IR. A pioneer in this field, G. Adams,[10] classified radiosensitizers into five groups based on the mechanisms of their action: (1) suppressors of intracellular thiols, or other endogenous radioprotective substances, (2) cytotoxic substances formed by radiolysis of the radiosensitizer, (3) inhibitors of DNA repair, (4) thymine analogs that can incorporate into DNA and (5) oxygen mimetics that can imitate the action of oxygen. However, the continuous development and innovation of new technologies and strategies of radiosensitization forced the introduction of a new classification into three categories based on sensitizer structures: (1) small molecules, (2) macromolecules, and (3) nanomaterials.(1)

Mechanisms of radioresistance involve tumor-specific oncogenic signalling pathways, tumor metabolism and proliferation, tumor microenvironment/hypoxia, and genomics. Most adenocarcinomas and sarcomas, advanced HNSCC, melanoma, non-SCLC, and gliomas are considered radioresistant. Radiosensitive tumors include myeloma, SCLC, germ cell tumors, PCa, and breast cancer.

In this review, we considered the use of radiosensitizers, including small molecules and nanomaterials, in various malignant tumors and the problems and prospects for their clinical use in cancer therapy.

Materials and Methods

We reviewed published data on radiotherapy and radiosensitization methods up to 2021, searching through PubMed, and references from relevant articles, using search terms with suitable keywords. The search terms were “cancer,” “ionizing radiation,” “cellular radiosensitivity,” “tumor tissue,” “DNA damage,” and “radioresistance.”

Drugs as Radiosensitizers in Different Types of Cancer

Breast cancer

Breast cancer is the most common cancer in women. Triple-negative breast cancer (TNBC) accounts for 10%-15% of all breast cancers. TNBC cells, characterized by the lack of estrogen and progesterone receptor expression, as well as HER2 amplification, are unresponsive to anti-ER or HER2 targeting agents. TNBC is the most aggressive subtype of breast cancer. Radioresistance and stemness are substantial obstacles to TNBC treatment. Lehmann et al. identified a LAR (luminal androgen receptor) subtype of TNBC, which included patients with decreased relapse-free survival and was characterized by androgen receptor (AR) signaling. LAR cell lines were uniquely sensitive to bicalutamide (an AR antagonist). AR is expressed in 15%–35% of all TNBC.[11] Michmerhuizen et al.[12] studied whether seviteronel (INO-464), a novel CYP17 lyase inhibitor and AR antagonist, can radiosensitize AR-positive (AR+) TNBC models. The authors reported that seviteronel could selectively radiosensitize AR+ TNBC models in vitro and in vivo. Radiosensitization was mediated, at least in part, through the delayed repair of dsDNA breaks. The results indicate AR as a mediator of radioresistance in AR+TNBC models and seviteronel as a radiosensitizing agent in AR+TNBC.

Lung cancer (LC)

Epigenetic alterations can be considered potential targets for radiosensitization. This can be achieved through the regulation of chromatin structure modifications or through epigenetic manipulations of genes involved in the cell cycle, apoptosis, or DNA repair. The available data on the association between epigenetics and radiosensitivity are sparse and are mostly based on in vitro or in vivo data.

A study by Kang et al.[13] aimed to elucidate the radiosensitizing effect and underlying mechanism of MA-17, a new kind of DNA methyltransferase (DNMT) inhibitor derived from a phthalimido alkanamide structure. DNMT expressions were confirmed in cultured human LC (A549) cells. MA-17 significantly radiosensitized A549 cells. Pretreatment with MA-17 increased sub-G1 fractions and inhibited the repair of double-strand breaks (DSBs) in DNA induced by irradiation. MA-17 also down-regulated DNA homologous recombination and the Fanconi anemia pathway (FANCA, BRCA1, and RAD51C) in A549 cells. DNMT inhibitor MA-17 possessed both biostability and favorable and substantial radiosensitizing effects by augmenting apoptosis or inhibiting DNA damage repair.

SCLC, a high-grade neuroendocrine carcinoma, makes up about 15% of LC cases. As an aggressive malignancy, SCLC has a critical need for novel therapies. Laird and colleagues[14] studied whether PARP inhibition could sensitize SCLC cells to IR. For radiosensitization, poly-ADP-ribose polymerases (PARP1/2) inhibitors veliparib and talazoparib were examined. Short-term viability assay and clonogenic survival assays were used to assess radiosensitization in 6 SCLC cell lines. Both PARP inhibitors effectively sensitize SCLC cell lines and PDXs to IR. However, talazoparib exhibited greater PARP-trapping activity that was associated with superior radiosensitization, and an increased number of

DNA DSBs. Thus, PARP inhibitors, especially those with high PARP-trapping activity, may improve the efficacy of radiotherapy in SCLC.

PARP1 and PARP2 are important DNA damage sensors as they bind rapidly at the site of DNA damage and help in resealing single-stranded DNA breaks during break excision repair and for the repair of the topoisomerase-1 cleavage complex.[15,17] Since PARP plays an important role in response to DNA damage, and radiation leads to double-stranded breaks, examining whether PARP inhibitors act synergistically with radiation is relevant.

Hastak et al.[18] examined the effects of a new PARP inhibitor, LT626, in combination with IR in lung and pancreatic cancers. The combination of LT626 with IR was more effective in inhibiting growth in lung and pancreatic cancer cell lines than either treatment used alone. Using in vivo LC xenograft models, the researchers demonstrated that LT626 functioned as an effective radiosensitizer during fractionated radiation treatment. Overall, in vitro and in vivo studies showed that LT626 acted synergistically with radiation in lung and pancreatic cancers.

Esophageal cancer

Esophageal cancer (EC) is divided into two subtypes, esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC). Altered mitochondrial function is linked with radioresistance in EAC. Buckley et al.[19] identified compounds with antiangiogenic and antimetabolic activity targeting oxidative phosphorylation to improve radiosensitivity in EAC cells from pyrazinib (P3)-containing molecules. The results show that in addition to reducing metabolic rates and levels of ROS in EAC, P3 improved radiosensitivity in an isogenic model of this cell type. P3, which had shown an antiangiogenic and antimetabolic effect in zebrafish, showed a reduction tested survival fraction of the cells. Furthermore, P3 also reduced the secretion of interleukins in cells with EAC. Further studies with P3 via EAC biopsies or other non-in vitro methods are important to elucidate the therapeutic potential of P3 further.

The enzyme ribonucleotide reductase (RR) contains the RRM2 subunit, whose overexpression is related to the cellular response to DNA damage, and this can lead to angiogenesis, metastasis, tumor progression, and drug resistance or radioresistance. Osalmid has been shown to inhibit RRM2 by binding to the latter's hydrogen bond. However, its radiosensitizing effects are unknown. In a study by Tang et al.,[20] RRM2 was found to be associated with acquired radioresistance in EC, and osalmid exerted direct cytotoxicity on EC cells. Immunofluorescence assays showed that osalmid treatments alone induce DNA DSBs. Moreover, an analysis by western blot showed that the combination of osalmid and IR induced many DSBs. Colony formation assays showed that osalmid treatment increased radiosensitivity in EC cells. Furthermore, the osalmid and irradiation combination significantly increased the apoptosis rate of EC cells, compared to irradiation or osalmid. Osalmid was identified to have antitumor effects and improved the therapeutic efficacy of radiation in EC.

Human epidermal growth factor receptor 2 (HER2) is involved in many types of cancer, including EC. Pirotinib is an irreversible inhibitor of HER2 that, in a novel experimental setting, has shown an antitumor effect in breast xenograft models that overexpress HER2. However, whether this drug can have an antitumor effect on the esophagus is still unknown. To this purpose, Lian et al.[21] performed a study to analyze the effect of pirotinib combined with radiotherapy on EC cells that were HER2-positive. The results showed that, unlike treatment with radiation alone, irradiated cells combined with pirotinib showed notably reduced colony formation; this indicated that pirotinib enhanced the radiation-inhibitory effect on colony formation in cell lines used. Pirotinib sensitized HER2-positive EC cells to radiation, which enhanced the antiproliferative effect of radiation. These findings are expected to provide a new strategy for the application of new drugs to treat EC.

ESCC tumors develop resistance to radiotherapy; this explains the metastasis, high recurrence, and poor five-year survival of patients with this condition. There are study reports that astaxanthin (ATX), a carotenoid family member, is a beneficial agent for therapy in many kinds of diseases due to its strong antioxidant property. It has had good results in treating various types of cancer. However, there still needs to be more information regarding the ATX effect on ESCC cells' radiosensitivity, and there are no reports yet on the exact mechanisms. To this end, a study by Qian et al.[22] was designed to discover if ATX could improve ESCC cells' sensitivity to irradiation and the possible mechanism in vitro, showing important evidence for this drug as a radiosensitizer in ESCC radiotherapy. ESCC cell lines were exposed to irradiation in the presence or absence of ATX treatment. It was shown that ATX improved the radiosensitivity of ESCC cells and induced apoptosis and G2/M arrest via inhibiting Bcl2, CyclinB1, Cdc2, and promoting Bax expression. ATX appears to be a novel radiosensitizer with promising results for the treatment of ESCC, and further research is warranted.

Sunitinib is a highly selective, multidirectional, receptor tyrosine kinase inhibitor; it has direct apoptotic and antiproliferative effects against various tumors. But there is very little information regarding radiosensitization in EC. Ding et al.[23] investigated the radiosensitive effects of sunitinib on human ESCC cells and the underlying mechanisms. ESCC cells were exposed to hypoxia and, before IR, were treated with sunitinib at different concentrations. Sunitinib enhances radiation-induced apoptosis in both normoxic and hypoxic ESCC cells. Compared with that of the hypoxia and IR groups, the apoptosis rate of the group treated with sunitinib increased dose-dependently. The authors found that the sunitinib radiosensitivity effect was associated with the downregulation of HIF-1α and VEGF expression and concluded that sunitinib could be a promising radiosensitizer for EC radiotherapy.

Prostatic cancer (PCa)

Genistein is a tyrosine-specific protein kinase inhibitor, the best-characterized bioflavonoid-based topoisomerase II poison, which inactivates EGFR, IGF1R, and Akt-mediated signaling. Type II topoisomerases generate double-stranded DNA breaks as part of their reaction mechanism.[24-27] Tyrosine kinase inhibitor (tyrphostin) AG1024 is a specific IGF1R inhibitor, and it has been reported that this inhibitor radiosensitizes prostate and breast cancer cells. Nevertheless, there is not

much information about PCa cells' radiosensitivity to combined treatment with AG1024 and genistein. To this end, Tang et al.[28] studied the synergistic effect of combined therapy with genistein and AG1024 on the PCa cell's radiosensitivity. Genistein treatment suppressed the homologous recombination (HRR) and the non-homologous end joining (NHEJ) pathways by inhibiting the expression of Rad51 and Ku70, and AG1024 treatment only inhibited the NHEJ-pathway via the inactivation of Ku70 detected in western blot analysis. Before irradiation, PCa cells were treated with AG1024, genistein, and a combination. The results show that the combined treatment with genistein and AG1024 improves X-radiation-induced apoptosis in the human PCa cell lines PC3 and DU145. Using western blot analysis, the authors detected the increased expression of ATM(Ser1981), Bax, and active caspase-3 and decreased expression of p-IGF1R(Tyr1135) and Bcl-2 in PC3 and DU145 cells treated with genistein (30 μM) and/or AG1024 (10 μM) plus X-irradiation. The results obtained suggest that both genistein and AG1024 induced apoptosis of PCa cells via the activation of apoptosis-related pathways, which may be associated with the inactivation of IGF1R, and the combination of genistein and AG1024 exhibited a synergistic effect on the radiosensitivity of PCa cells by suppressing the HRR and NHEJ pathways.

Colon cancer

Imidazoacridinone C-1311 is a multipurpose therapeutic agent tested in patients with advanced solid tumors. It was found that C-1311 possesses an acceptable toxicity profile. C-1311 inhibits topoisomerase, leading to subsequent DNA strand breaks and the formation of cleavable complexes of DNA-topoisomerase II complexes. Skwarska et al.[29] conducted a study to assess the effect of the p53 tumor suppressor on the biological response to C-1311 using the genetically matched pair of human colon carcinoma cell lines, HCT116p53+/+ and HCT116p53−/−. Using human colon cancer cell lines, the authors provided a molecular analysis of the response to C-1311 exposure and showed that cells with wild-type p53 underwent p53-mediated G2 phase arrest and, ultimately, senescence; in contrast, cells lacking p53, despite an initial arrest in G2, entered mitosis and underwent mitotic catastrophe and apoptosis. In addition, cells in hypoxic conditions also responded to C-1311 in a p53-dependent manner. The most important result was that C-1311 can be effectively combined with radiation to improve the radiosensitivity of a panel of cancer cell lines.

Lithium chloride (LiCl) is a specific glycogen synthase kinase (GSK)3β inhibitor. This medicine is helpful in treating neurological diseases, cancer, and inflammation. Cammarota et al.[30] investigated the effect of LiCl treatment on the viability of primary colon cancer cells exposed to 7 Gy delivered by highenergy photon beams. To achieve this aim, the viability of irradiated T88 cells, mesenchymal colon cancer cells, was compared with that of irradiated T88 cells pretreated with LiCl. The authors demonstrated that T88 mesenchymal colon cancer cells are resistant to radiotherapy, and LiCl sensitizes these cells to apoptosis in response to high-energy photons. The decrease in cell viability was greater with combined therapy than with irradiation alone. The authors concluded that LiCl could be used to increase the sensitivity of resistant colon cancer cells to radiotherapy.

Celecoxib is a nonsteroidal anti-inflammatory drug, specifically a COX-2 inhibitor. Celecoxib showed anti-cancer effects in both COX-2 dependent and independent pathways and is used as a radiosensitizing enhancer. BI-69A11 is an ATP-competitive AKT inhibitor. Because both COX-2 and AKT inhibitors can enhance the effects of radiation on cancer cells, it is believed that combined treatment of both inhibitors may significantly radiosensitize cancer cells. Pal and colleagues[31] did research in which the effects of combined treatment with celecoxib and BI-69A11 on the colon cancer cells' radiosensitivity were evaluated to define whether this combination is beneficial for patients treated with radiotherapy. Triple therapy treatment led to the induced activation of apoptotic pathways. The authors revealed the therapeutic potential of triple combination therapy in the prevention of radioresistance and demonstrated the cytotoxic effects of triple combination therapy in colon cancer.

Pancreatic ductal adenocarcinoma (PDAC)

Gemcitabine is an antineoplastic agent currently used to treat several types of cancer, including pancreatic cancer. The use of gemcitabine as a radiosensitizer has shown promising results. In different experimental models, the p38 MAPK signaling pathway has been shown to be a major determinant in the cellular response to gemcitabine. However, the molecular mechanism implicated in gemcitabine-associated radiosensitivity remains to be investigated. A study by Pascual-Serra et al.[32] showed that the specific knockdown of MAPK11 (p38β) induced a total loss of the radiosensitivity associated with gemcitabine, as well as a marked increase in the resistance to the drug. The authors identified p38β as a major determinant of the radiosensitizing potential of gemcitabine.

Gemcitabine is widely used as a radiosensitizer for PDAC treatment and is known to induce S-phase arrest of tumor cells, which is a cell cycle phase known to sensitize cells to DNA damage, one of the mechanisms of cell death induced by radiotherapy**.** Waissi et al.[33] performed an in vivo study and a whole-transcriptome analysis to determine whether treatment with gemcitabine, combined with proton therapy and reinforced by DNA-damage radiosensitization using a PARP inhibitor, olaparib, is a viable strategy to improve the treatment of PDAC. NMRI mice bearing MIA PaCa-2 xenografts were treated with olaparib and/or gemcitabine and irradiated with 10Gy photon or proton. The results obtained showed that the association of gemcitabine, olaparib, and proton therapy significantly enhanced tumor response and progression-free survival in a heterotopic xenografts mice model.

Vance et al.[34] demonstrated that combined inhibition of homologous recombination repair mediated by checkpoint kinase-1 [Chk1] via AZD7762 and PARP1 [via olaparib (AZD2281)] selectively radiosensitizes p53 mutant pancreatic cancer cells.

Nasopharyngeal carcinoma (NPC)

Salinomycin is a monocarboxylic polyether antibiotic that kills many types of microorganisms. It has also shown

great efficacy in killing cancer stem cells. However, the information on radiosensitivity is rare. A study by Zhang et al.[35] aimed to explore the radiosensitivity of salinomycin on human NPC cell line CNE-2. CNE-2 cells were treated with salinomycin or irradiation, alone or in combination. DSB levels were determined by γ-H2AX foci immunofluorescence staining in CNE-2 cells at different time points after X-ray exposure. The combination of salinomycin treatment and 4-Gy X-rays increased γ-H2AX nuclear foci formation, compared with X-rays alone. Nuclear foci without salinomycin increased due to DBS repair. Salinomycin induced apoptosis and G2/M arrest, increased Bax and cleaved caspase3, decreased Bcl-2 expression, and increased the formation of γ-H2AX nuclear foci. The authors concluded that salinomycin may be a radiosensitizer for NPC radiotherapy.

Liver cancer

HCC is the most common form of liver cancer and the third most common cause of cancer deaths worldwide. Some studies have reported that chemotherapy agents can be used as radiation sensitizers in the treatment of HCC.[36,37] The phenanthroline derivatives and their metal complexes have been recognized as potential anticancer candidates because they have a strong affinity with DNA and are safer and more efficient for further cancer therapy.[38] Liu et al.[39] synthesized a phenanthroline derivative, 2-phenyl-imidazo [4, 5 f] [1, 10] phenanthroline (L02), and combined it with X-ray radiation to investigate whether it can enhance the radiosensitivity in inhibiting HCC cells. The radiosensitization of L02 combined with IR was evaluated by the sensitivity enhancement ratio and isobolographic analysis. L02 sensitized HCC cells to IR by inducing apoptosis, increasing the expression of apoptosis markers, and enhancing radiation-induced DNA damage. The authors concluded that L02 may be a novel radiosensitizer for HCC.

Apatinib, a highly selective inhibitor of the vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase, has a good inhibitory effect on advanced HCC.[40] In HCC, apatinib can induce cell cycle arrest at the G2/M phase, promoting apoptosis of HCC cells in vitro, and its inhibitory effect is related to the expression level of VEGFR.[41] In SMMC-7721 cells, apatinib promoted apoptosis by inhibiting the phosphorylation level of PI3K/AKT.[42] The combination of this drug with chemotherapy and immunotherapy has shown progress. Liao et al.[43] investigated the potential clinical utility of apatinib as a radiosensitizer in the treatment of HCC. The findings revealed that apatinib enhanced the radiosensitivity of HCC cell lines, suppressed the repair of radiation-induced DNA DSBs, and increased IR-induced apoptosis. Apatinib radiosensitized HCC via suppression of the IR-induced PI3K/AKT pathway. In an in vivo study, apatinib combined with irradiation significantly decreased xenograft tumor growth. Apatinib showed therapeutic potential as a radiosensitizer in HCC suppressing PI3K/AKT signaling pathway.

Head and neck cancer

Most head and neck cancers are squamous cell cancers. Human papillomavirus (HPV) is a known risk factor for head and neck squamous cell carcinoma (HNSCC). p16 immunohistochemistry is a widely used method to detect HPV positivity in cancer. The tumor suppressor gene p16, encoding a specific inhibitor of cyclin-dependent kinase (CDK) 4 and 6, is found to be altered in various cancers. It is thought that expression of p16 in HPV-positive HNSCC mediates radiosensitivity via inhibition of CDK 4/6. Göttgens and colleagues[44] used a clinically approved CDK4/CDK6 inhibitor, palbociclib, and assessed its effect on radiosensitivity in HPV-negative and HPV-positive HNSCC cell lines. The study results showed that only HPV-negative HNSCC cells were radiosensitized by palbociclib, which was dependent on the presence of hyperphosphorylated retinoblastoma protein. Palbociclib was an effective radiosensitizer at hypoxia levels that are associated with radiation resistance. The combination of IR and palbociclib was highly effective, leading to the loss of cell viability and a failure to repair IR-induced DNA damage and subsequent mitotic catastrophe. The combination of palbociclib and IR may be an effective therapeutic strategy for treating HPV-negative HNSCC.

Bladder cancer (BC)

Approximately 70% of bladder tumors are nonmuscle-invasive BC; the rest are muscle-invasive BCs. Muscle-invasive BC (MIBC) is more aggressive than non-invasive disease, and approximately 50% of patients with this disease will experience distant recurrence following therapy. Inhibitors of HDAC have been identified as an effective strategy to enhance cancer radiotherapy HDAC inhibitors (HDACi) decrease the ability of tumor cells to repair radiation-induced DNA damage by interfering with DNA damage signalling and repair pathways.[45] In a study by Tsai et al.,[46] the selective HDAC6i enhanced BC radiosensitization and effectively inhibited IR-induced oncogenic CXCL1-Snail-signalling.

Paillas et al.[47] studied the HDAC class I-selective agent romidepsin as a radiosensitizer in bladder tumors. In vitro, romidepsin effectively radiosensitized different BC cells. Romidepsin in combination with IR resulted in a significant delay in tumor growth and did not increase the severity of acute (3.75 days) and late toxicity (at 29 weeks). of normal intestinal tissues. The authors suggest that the disruption of DNA repair pathways caused by romidepsin is a key mechanism for its radiosensitizing effect in BC cells.

Several studies have indicated that tumor survival and growth in advanced cancers are related to autophagy. Autophagy helps tumor cells to overcome stressful conditions, including hypoxia and nutrient deprivation. The inhibition of autophagy or knockdown of autophagy genes can result in tumor-cell death.[48,49] The relationship between radiotherapy and autophagy has not been studied in depth. As apoptosis only accounts for 20% or less of radiation-induced cell death, other cell death pathways, including autophagy, should also be studied.[50]

A study performed by Wang et al.[51] aimed to investigate the radiosensitizing effect of chloroquine in BC, with an emphasis on autophagy inhibition and apoptosis induction. BC cell lines were irradiated with or without chloroquine. The apoptosis rate was measured using Annexin V-FITC/PI double staining. To evaluate the activity of autophagy, the LC3 II and p62 levels were detected with western blotting analysis. Radiation-induced DNA DSBs were measured by

the staining of γ-H2AX. Chloroquine alone inhibited the proliferation of BC cells in a dose-dependent manner. Low cytotoxic concentrations of chloroquine enhanced the radiation sensitivity of BC cells. Chloroquine also decreased the repair of radiation-induced DNA damage. The accumulation of LC3 II and p62 protein levels in BC cell lines was increased by chloroquine treatment. After irradiation, the expression of LC3 II increased, whereas the p62 protein level decreased, which suggested that irradiation activated autophagy. The expression levels of LC3 II and p62 in the combined treatment group were higher than in irradiation alone, indicating that chloroquine inhibited autophagy induced by irradiation in BC. Inhibiting autophagy and activating apoptosis, chloroquine might be a promising radiosensitizer in the radiation therapy of BC.

Anticancer drugs and the mechanism of their action at the cellular/molecular level are summarized in Table 1.

Nanoparticles and small molecule inhibitors

In the past decade, there has been considerable interest in radiosensitization using high atomic number (high-Z) metal nanoparticles (NPs).[52,53] Since high-Z metal NPs have a higher stopping power for IR than soft tissue, they enhance radiotherapy efficacy.[54,55] An enhanced therapeutic effect by radiosensitization mediated by high-Z metal NPs has been reported in multiple preclinical tumor models, including glioblastoma multiforme.[55] Stewart et al.[56] provided the first proof for the novel application of bismuth oxide (Bi2O3) as a radiosensitizer on the highly radioresistant 9L gliosarcoma cell line. The results showed that Bi2O3 NPs increase the radiosensitivity of 9L gliosarcoma tumor cells for both kVp and MV energies.

Saberi et al.[57] evaluated the effect of gold nanoparticles (GNPs) on radiosensitization enhancement of HT-29 human colorectal cancer cells at megavoltage (MV) X-ray energy.

Table 1.

Anticancer agents and the mechanism of their action at the cellular/molecular level.

Agents	Action	Source
Huaier	G0/G1 phase cell cycle arrest	Ding et al. (2016) [78]
Seviteronel	Accumulation of DNA DSBs	Michmerhuizen et al. (2020) [13]
MA-17	Inhibition of DNMT	Kang et al. (2019) [14]
Talazoparib	Enzyme inhibition and PARP trapping	Laird et al. (2018) [15]
Tanshinone I	Differential protein expression	Yan et al. (2018) [93]
Diosmetin	Inhibition the activated Akt signaling pathway	Xu et al. (2017) [97]
Pyrazinib	Reduction of ROS levels	Buckley et al. (2019) [20]
Osalmid	Induction of DNA DSBs	Tang et al. (2020) [21]
Sunitinib	Downregulation of HIF-1α and VEGF expression	Ding et al. (2016) [24]
Pirotinib	Innhibition of HER2	Lian et al. (2020) [22]
Astaxanthin	Antioxidant property, G2/M phase cell cycle arrest	Qian et al. (2017) [23]
Genistein	Activation of apoptotic pathways, suppression of the HRR and NHEJ pathways	Tang et al. (2018) [29]
Sinomenine hydrochloride	Suppression of expression of double-strand break repair protein Ku80 and Rad51 and enhancing Chk1 activation	Zhang et al. (2018) [80]
Imidazoacridinone C-1311	Topoisomerase inhibition	Skwarska et al. (2017) [30]
lithium chloride	GSK-3β inhibition, induction of apoptosis	Cammarota et al. (2020) [31]
Celecobix	COX2 inhibition, activation of apoptotic pathways	Pal et al. (2016) [32]
BI-69A11	ATP-competitive AKT inhibitor	Pal et al. (2016) [32]
Kaemferol	Reduction of clonogenic survival	Kuo et al. (2015) [94]
Gencitabine	Tumor cell's S-phase arrest	Pascual-Serra et al. (2021) [33]
Salinomycin	Induction apoptosis and G2/M phase cell cycle arrest	Zhang et al. (2016) [36]
Phenanthroline L02	Induction apoptosis	Liu et al. (2019) [40]
Apatinib	Suppression of IR-induced PI3K/AKT pathway	Liao et al. 2019 [44]
Mesima	Induction of apoptosis, impairment of cell cycle regulation, reduction of IR-induced DNA damage repair.	Jeong et al. (2020) [92]
Palbociclib	CDK4/6 inhibition	Göttgens et al. (2019) [45]
Romidepsin	Disruption of DNA repair pathways	Paillas et al. (2020) [48]
Valproate	HDAC inhibition	Stritzelberger et al. 2020 [98]
Chloroquine	Inhibition of autophagy and activation of apoptosis	Wang et al. (2018) [52]
Lys05	Lysosomal membrane permeabilization and mitochondrial depolarization.	Zhou et al. (2020) [99]
PI-103	Inhibition of Hsp90	Djuzenova et al. (2012) [105]

The findings showed that the cell viability was not influenced by exposure to different concentrations of GNPs (10-100 μM). GNPs alone did not affect the cell cycle progression and apoptosis. In contrast, GNPs, in combination with 9MV radiation, induced more apoptosis. The interaction of GNPs with MV energy resulted in a significant radiosensitization enhancement, compared with IR alone. The authors concluded that GNPs can act as a bioinert material on NT-29 cancer cells, and enhancing radiosensitization may be associated with an increase in the absorbed radiation dose.

Habiba et al.[58] developed a new type of silver nanoparticle composite, PEGylated graphene quantum dot (GQD)-decorated Silver Nanoprisms (pGAgNPs), that show excellent in vitro intracellular uptake and radiosensitization in radiation-sensitive HCT116 and relatively radiation-resistant HT29 colorectal cancer cells. Treatment with nanoparticles and a single radiation dose of 10Gy significantly reduced the growth of colorectal tumors in nude mice and increased the survival time compared to treatment with radiation only.

The development of safe nanoparticle-based drug carriers to administer the drug directly into tumors and keep it there longer is of great interest. Mirjolet et al.[59] investigated titanate nanotubes (TiONts) to develop a TiONts-docetaxel (DTX) nanocarrier and to evaluate its radiosensitizing efficacy in vivo in a PCa mouse model. Tumor growth was significantly slowed by TiONts-DTX with IR, compared with free DTX in the same conditions. These results suggest that TiONts-DTX improved radiotherapy efficacy in PCa.

Over the past few decades, small molecule inhibitors (SMIs) have gained acceptance as new therapeutic strategies in cancer. SMIs are compounds less than 500Da, targeting any part of the molecule, regardless of the location of the target in the cell.[60] Flap endonuclease 1 (FEN1), a structure-specific metallonuclease, is a typical member of the Rad2 nuclease family. FEN1 plays a critical role in the maturation of the Okazaki fragment of DNA replication. It is essential to DNA repair pathways, such as base excision repair and the polymerase α error editing (AEE) pathway.[61-64] FEN1 is overexpressed in many forms of cancer, and FEN1 inhibitor has been reported to enhance the effect of DNA damage-related chemotherapy.[65-66] The purpose of a study conducted by Li et al.[67] was to determine whether FEN1 inhibitor SC13 could enhance the therapeutic effect of IR therapy in cervical cancer. The results revealed that FEN1 is overexpressed in HeLa cells and can be upregulated further by IR. It was demonstrated that FEN1 inhibitor SC13 enhances IR sensitivity of cervical cancer in vitro and in vivo, and the beneficial effect was mainly due to the impairment of the DNA damage repair mechanism resulting from FEN1 inhibition, leading to apoptosis of cancer cells.

To date, evidence has been accumulated that small non-coding RNAs, microRNAs (miRNAs), are involved in regulating tumor initiation and progression.[68-72] Some studies demonstrated that miRNAs can be used as radiosensitizers.[72,73] Baek et al.[74] showed that overexpression of miR-374 sensitized human pancreatic cancer cell lines PANC1 and MIA PaCa-2 toward carbon ion beam radiation. miRNA miR-374 can potentially be a new radiosensitizer for carbon ion beam radiotherapy.

The mechanisms of the actions of nanoparticles (NP) and small molecule inhibitors (SMI) are summarized in Table 2.

Table 2.

Nanoparticles (NP) and small molecule inhibitors (SMI) and the mechanism of their action.

NP/SMI	Action	Source
Bi2O3	Increasing sensitivity for both kVp and MV energies	Stewart et al. (2016) [57]
miR-374	Increasing sensitivity to carbon ion beam radiation	Baek et al. (2016) [76]
Gold NPs	Increasing the absorbed radiation dose.	Saberi et al. (2017) [58]
TiONts	Reducing tumor growth	Mirjolet et al. (2017) [60]
Silver NPs (pGAgNPs)	Reducing tumor growth	Habiba et al. (2019) [59]
FEN1 inhibitor SC13	Impairment of the DNA damage repair	Li et al. (2019) [69]

Actions of certain drugs toward apoptotic pathways and cellular mechanisms linked to cancer, as well as targets of drugs and compounds are presented in Images 2 and 3.

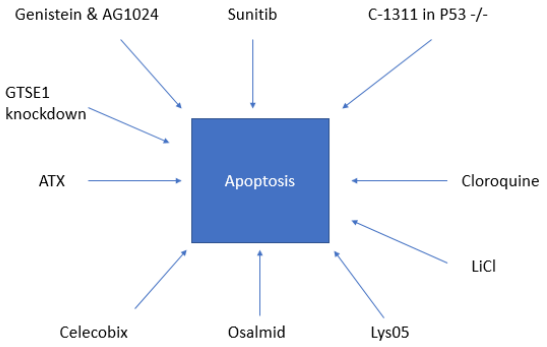

Image 2. *Actions of anticancer drugs toward apoptotic pathways and cellular mechanisms linked to malignant tumors.*

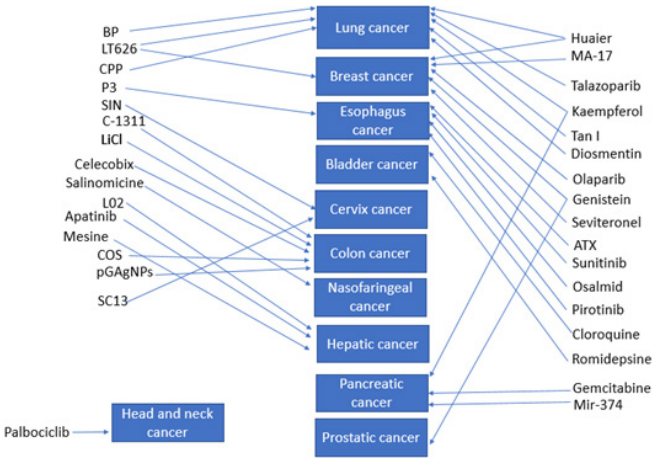

Image 3. *Targets of anticancer drugs and compounds.*

Medicinal plants and traditional Chinese medicine

Recently, several natural products showed promising anticancer properties. Huaier (*Trametes robiniophila Murr*) is a medicinal fungus of traditional Chinese medicine with more than 1500 years of history of clinical application. In recent years, potent antitumor effects of Huaier have been noted in various neoplastic diseases, including breast cancer, HCC, lung cancer, and gastrointestinal cancer.[75] Ding and colleagues[76] conducted a study to evaluate the combined effects of radiotherapy and Huaier on breast cancer. Using HTA 2.0 transcriptome microarray assay, the researchers found that Huaier downregulates genes related to the cell cycle, cell division, cell cycle phases, and DNA repair. The findings obtained suggest that Huaier causes G0/G1 arrest through downregulation of cell cycle-regulating proteins in MCF-7 and MDA-MB-468 cells, prolongs the persistence of γ-H2Ax foci after radiotherapy, and interferes with the homologous recombination pathway of DNA repair by downregulating RAD51. Thus, Huaier may be a promising radiosensitizer for treating breast cancer.

N-Butylidenephthalide (BP), extracted from traditional Chinese medicine *Radix Angelica Sinensis* (*Danggui*), shows antitumor activity against various cancer cell lines. Su et al.[77] studied BP's cytotoxic and radiosensitizing effects in human breast cancer cells. The terminal deoxynucleotidyl transferase dUTP nick end labeling staining (TUNEL assay) detected that BP induces apoptosis in breast cancer cells. BP increased the radiosensitivity of breast cancer cells as measured by colony formation assay and comet assay. The authors concluded that BP could be a potential chemotherapeutic and radiosensitizing agent for the treatment of breast cancer.

Sinomenium acutum has been used in the treatment of neuralgia and rheumatoid arthritis in Asia since ancient times. Sinomenine (SIN), a bioactive alkaloid extracted from the Chinese medicinal plant *Sinomenium acutum*, has many healing properties both in vivo and in vitro. However, the SIN anticancer effects and its water-soluble form, sinomenine hydrochloride (SH), have been recently characterized. Zhang D. and collaborators [78] assessed the sensitizing efficacy of SH in human cervical cancer cells to irradiation, and demonstrated it is a potential radiosensitizer. The results of the study showed that SH treatment affects the DNA DSB response in cells. Likewise, SH was found to suppress the DSB repair protein Ku80 and Rad51 expression and enhance Chk1 activation induced by irradiation. The results showed that SH was useful in radiosensitization through dual pathways, regulation of cell cycle checkpoint, and DNA repair.

Zhang et al.[80] investigated the radiosensitizing effect and underlying mechanisms of *Cyclocarya paliurus* (CP) polysaccharide (CPP) on hypoxic A549 and H520 human nonsmall cell lung carcinoma cells. CP is a member of the Juglandaceae family. CPP is a heteropolysaccharide that possesses antioxidant and hypoglycemic effects and antitumor activity.[80-82] The study's results suggested that CPP markedly inhibited the viability of hypoxic A549 and H520 cells. Combined treatment with CPP and IR enhanced apoptosis of hypoxic A549 and H520 cells, suppressed cell proliferation, modified the expression levels of hypoxiainducible factor1α, survivin, cleaved caspase3, and affected the mammalian target of rapamycin (mTOR)/Akt/phosphatidylinositol4,5bisphosp hate 3kinase (PI3K) pathway. The potential radiosensitizing effects of CPP suggest its efficacy in the combined treatment of non-small cell lung carcinoma.

Phellinus linteus (Mesima), a tropical basidiomycete fungus, is used extensively as a traditional medicine in China, Korea, and other Asian countries to treat different diseases, including many human malignancies.[83,84] The main biological functions of *P. linteus* include anticancer, antioxidant, anti-inflammatory, hypoglycemia, and anti-fibrotic.[85-89] Jeong et al.[90] examined its potential as a radiosensitizer in HCC radiotherapy using human HCC Hep3B and HepG2 cell lines and xenograft tumors. Mesima pretreatment significantly enhanced HCC cell radiosensitivity in vitro, and Mesima+IR significantly reduced xenograft tumor growth and size in vivo compared to those with single treatments. Mesima significantly enhanced radiotherapy efficiency by inhibiting tumor cell survival, inducing apoptosis, impairing cell cycle regulation, and reducing radiation-induced DNA damage repair. The cell viability rate was reduced significantly for cells treated with Mesima before irradiation than those without Mesima. The authors demonstrated that the combined treatment likely regulated the apoptotic process, including intracellular caspase signaling. These findings support the radiosensitizing effects of Mesima on HCC cells.

Tanshinone I (Tan I) is a natural product from *Salvia miltiorrhiza*, showing a broad spectrum of bioactivities, including antitumor activity. Yan et al.[91] identified Tan I as a potential radiation sensitizer in LC cells. Tan I significantly inhibited cell proliferation and clone formation by increasing radiosensitivity in radioresistant LC cells, H358-IR and H157-IR. Tan I suppressed the expression of the pro-oncogenic protein phosphoribosyl pyrophosphate aminotransferase (PPAT) in H358-IR and H157-IR cells and integrated well into the active pocket of the PPAT structure, acting as a potential PPAT inhibitor and improving radiation efficiency.

Kaempferol is a flavonol in the flavonoid category and is widely distributed in various plant genera, such as delphinium, camellia, barberry, and citrus fruits, Kaempferol has been reported to be effective against human non-small cell lung carcinoma, pancreatic cancer, and glioma cells. Nevertheless, the combination of kaempferol and radiation against cancer is still being evaluated. Kuo et al.[92] studied the potential radiosensitization ability of kaempferol in LC in vitro and in vivo. After administering kaempferol, cells were exposed to 0 to 12Gys of radiation. Treatment of cells with radiation alone was found to have a minimal effect on clonogenic survival. However, when kaempferol was administered before irradiation, the surviving fraction significantly decreased. In an in vivo study, it was observed that the volume of the tumor decreased when there was a combination of kaempferol and irradiation. This study provided strong evidence that kaempferol has potential as a radiosensitizer.

The protein kinase B signaling pathway (PKB/Akt), hyperactivated during oncogenesis, is a candidate target for cancer therapy.[93] Akt, as an important intracellular signaling molecule, is critical for cell survival and growth, especially

during cancer progression and radioresistance.[94] Xu et al.[95] showed that diosmetin, the aglycone of the flavonoid glycoside from olive leaves, citrus fruits, and some medicinal herbs, has a promising effect on radiotherapy sensitization. Diosmetin could induce G1 phase arrest and thus enhance the radiosensitivity of radioresistant A549/IR LC cells. Diosmetin also restrains the IR-induced DNA damage repair by inhibiting the activated Akt signaling pathway, acting as a potential drug for treating radioresistant LC cells.

Miscellaneous

Valproate (VPA) is an antiepileptic that, in addition to its anticonvulsant properties, is an effective HDACi, which participates in the modulation of chromatin structure and gene expression. VPA increases radiation sensitivity in various tumor cells in vitro. However, clinical data on the possible improvement of tumor control by adding VPA to tumor therapy is controversial. To determine individual radiosensitivity, Stritzelberger et al.[96] analyzed blood samples of individuals taking VPA. Ex vivo irradiated blood samples of 31 adult individuals with epilepsy were studied using 3-color fluorescence in situ hybridization. Aberrations in chromosomes 1, 2, and 4 were analyzed. Radiosensitivity was determined by the mean number of breaks per metaphase (B/M) and compared with healthy donors of the same age. The average B/M value was higher in the patient group than in healthy individuals (0.480±0.09 vs. 0.415±0.07; P=0.001). The portion of radiosensitive (B/M>0.500) and distinctly radiosensitive (B/M>0.600) individuals was increased in the VPA group (54.9% vs. 11.3% and 9.7% vs. 0.0%; P<0.001). The authors confirmed that patients treated with VPA had an increased radiosensitivity, compared to the control group.

Hydroxychloroquine (HCQ) is a drug that shows effectiveness in many types of tumors. Lys05, dimeric chloroquine, is a newly synthetic lysosomotropic agent that accumulates in the lysosome and blocks autophagy more potently than hydroxychloroquine. Zhou and colleagues [97] studied whether Lys05 has anti-glioma activity. The researchers found that Lys05 decreased cell viability and reduced cell growth of glioma U251 and LN229 cells. After Lys05 treatment, autophagic flux was inhibited and lysosome function was impaired. In addition, Lys05 caused lysosomal membrane permeabilization (LMP) and mitochondrial depolarization. It was concluded that Lys05 increased radiosensitivity in an LMP-dependent manner.

Over the last decade, heat-shock protein 90 (Hsp90) has gained increasing interest as a promising anticancer drug target.[98,99] Hsp90 inhibitors can enhance the sensitivity of tumor cells to the effect of IR in vitro. Several studies have identified Hsp90 as a potential molecular target for radiosensitization.[100,101] Stingl et al.[102] showed that NVP-AUY922, a novel inhibitor of Hsp90, enhances the effect of IR on tumor cells under normoxic conditions. In a study by Djuzenova CS et al.,[103] the clonogenic assay revealed that in lung carcinoma A549 and glioblastoma SNB19 cell lines, NVP-AUY922 enhanced the radiotoxicity under hypoxic exposure to a level like that observed under oxic conditions. These findings may have implications for the combined modality treatment of solid tumors.

Kudryavtsev et al.[104] studied the role of the inducible Hsp70 in the cellular response to radiosensitizing treatments with the Hsp90 inhibitors. Cell lines derived from solid tumors of different origins were treated with the Hsp90 inhibitors or/and γ-photon radiation. The authors found that the Hsp90 inhibitors yielded considerable radiosensitization only when they caused early and pronounced Hsp70 induction; moreover, a magnitude of radiosensitization was positively correlated with the level of Hsp70 induction. It is obvious that targeting the Hsp70 induction in Hsp90 inhibitor-treated cancer cells may enhance the radiosensitivity of tumor cells.

There are many reports on the anticancer effects of chitooligosaccharides (COS);[105-108] however, there is very little information on their radiosensitizing effects. Han et al.(109) investigated the anti-proliferation and radiosensitization effect of COS on human colon cancer cell line SW480. The RAY+COS group was treated with 1.0mg/mL of COS for 48h; the RAY and RAY+COS groups were exposed to X-ray at 0, 1, 2, 4, 6, and 8Gy, respectively. The apoptosis rate was significantly higher in the RAY+COS group than in the RAY group. The percentage of cells in the G2/M phase was higher, and the percentage of cells in the S phase and G0/G1 phase was lower in the RAY+COS group than in the RAY group. The study indicated that COS can enhance the radiosensitization of SW480 cells, inducing apoptosis and G2/M phase arrest.

Alternative diagnostic approaches and new therapeutic strategies in cancer treatment

Over time, more evidence has been discovered that radiosensitizing effects may be genotype-dependent, requiring predictive biomarkers for proper patient selection. Unfortunately, survival clonogenic assays are not suitable for the large cell lines that would be needed to identify tumor genotypes correlated with sensitivity to IR/drug combinations due to the poor ability of the human cancer cell lines to form colonies and the paucity of resources to conduct these assays. Liu Q. et al.[110] hypothesized that short-term assays could provide a change measure of the change in cellular radiosensitivity caused by a targeted drug if the drug, within a few days following irradiation, alters the cell inactivation mode, such as senescence, apoptosis, or autophagy. The authors conducted screening of 32 cancer cell lines using 18 targeted therapeutic agents with known or putative radiosensitizing properties. The cell number remaining after drug exposure with or without radiation was assessed by nonclonogenic assays. To genetically screen for mechanisms of radiosensitization of the multi-kinase inhibitor midostaurin, the drug was administered to 5 LC cell lines. Four of the top 5 cell lines radiosensitized by midostaurin (SRF2Gy of 1.02–1.13) harbored KRAS mutations in codons 12 and 13. In contrast, cells with wild-type KRAS did not show radiosensitization. KRAS mutations (codons 12/13) were found to be a biomarker of radiosensitization by midostaurin in LC. Data highlight the potential clinical significance of this type of screening.

Cyclin-dependent kinases (CDKs) are key regulatory enzymes involved in cell proliferation. They regulate cell cycle checkpoints and transcriptional events in response to extracellular and intracellular signals. The crucial function of

CDKs in cell cycling and DNA damage repair and frequent aberrations of their activities in cancer encouraged an intensive screening for small-molecule CDK inhibitors. CDK9 is one of the most important transcription regulatory members of the CDK family. Storch et al.[111] evaluated the significance of CDK9 inhibition using siRNA technology and a multi-target tumor growth inhibitor ZK 304709 for the radioresponse in a panel of HNSCC cell lines. Upon either CDK9 small interfering RNA knockdown or treatment with ZK304709, the authors examined colony formation, DNA DSBs, apoptosis, cell cycling, and expression and phosphorylation of major cell cycle and DNA damage repair proteins. The results indicated that CDK9 overexpression mediated radioprotection; in contrast, CDK9 depletion enhanced the radiosensitivity of HNSCC cells without induction of apoptosis. ZK304709 showed concentration-dependent cytotoxicity but failed to radiosensitize HNSCC cells. The authors suggested a potential role of CDK9 in the radiation response of HNSCC cells.

G2 and S phase-expressed 1 (GTSE1), a cell cycle-related protein regulating G1/S cell cycle transition,[112] is also closely associated with DNA repair. The response of GTSE1 to IR remains uncovered. A study by Lei et al.[113] aimed to elucidate the radiosensitizing effects in non-SCLC via knockdown GTSE1 expression. The researchers found that radiation could induce GTSE1 to be recruited to DSB site and initiate DNA damage response. The knockdown of GTSE1 expression in non-SCLC cells by siRNA significantly inhibited the proliferation, promoted apoptosis after IR, and enhanced radiosensitivity in NSCLC, impairing the DNA damage repair process.

Conclusion

Recently, radiotherapy has developed rapidly, taking on an increasingly prominent role and position in cancer treatment. Improving radio response with radiosensitizers is a promising approach. Several strategies have been used to develop highly effective and low toxicity radiosensitizers, including small molecules, macromolecules, and nanomaterials. Manipulation of genes involved in radiation resistance represents an important approach to therapeutic intervention in cancer. The combination of radiotherapy with gene therapy provides a promising strategy to modify the radiation response and overcome the radioresistance of tumor cells. However, despite significant advances in the development of radiosensitizers, there is a need to search for new targets for radiotherapy and new mechanisms of sensitization, as well as the development of more effective radiosensitizing drugs.

Competing Interests

The author declares that there is no conflict of interest.

References

1. Wang H, Mu X, He H, Zhang XD. Cancer Radiosensitizers. Trends Pharmacol Sci. 2018 Jan;39(1):24-48. doi: 10.1016/j.tips.2017.11.003.

2. Telarovic I, Wenger RH, Pruschy M. Interfering with Tumor Hypoxia for Radiotherapy Optimization. J Exp Clin Cancer Res. 2021 Jun 21;40(1):197. doi: 10.1186/s13046-021-02000-x.

3. Crabtree HG, Cramer W. The action of radium on cancer cells. II.—Some factors determining the susceptibility of cancer cells to radium. Proc R Soc Lond Ser B Contain Pap Biol Character. 1933;113(782):238–50. doi.org: 10.1098/rspb.1933.0044.

4. GRAY LH, CONGER AD, EBERT M, HORNSEY S, SCOTT OC. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol. 1953 Dec;26(312):638-48. doi: 10.1259/0007-1285-26-312-638.

5. Moeller BJ, Richardson RA, Dewhirst MW. Hypoxia and radiotherapy: opportunities for improved outcomes in cancer treatment. Cancer Metastasis Rev. 2007 Jun;26(2):241-8. doi: 10.1007/s10555-007-9056-0.

6. Rofstad EK, Gaustad JV, Egeland TA, Mathiesen B, Galappathi K. Tumors exposed to acute cyclic hypoxic stress show enhanced angiogenesis, perfusion and metastatic dissemination. Int J Cancer. 2010 Oct 1;127(7):1535-46. doi: 10.1002/ijc.25176.

7. Bhaskara VK, Mohanam I, Rao JS, Mohanam S. Intermittent hypoxia regulates stem-like characteristics and differentiation of neuroblastoma cells. PLoS One. 2012;7(2):e30905. doi: 10.1371/journal.pone.0030905.

8. Martinive P, Defresne F, Bouzin C, Saliez J, Lair F, Grégoire V, et al. Preconditioning of the tumor vasculature and tumor cells by intermittent hypoxia: implications for anticancer therapies. Cancer Res. 2006 Dec 15;66(24):11736-44. doi: 10.1158/0008-5472.CAN-06-2056.

9. Minassian LM, Cotechini T, Huitema E, Graham CH. Hypoxia-Induced Resistance to Chemotherapy in Cancer. Adv Exp Med Biol. 2019;1136:123-139. doi: 10.1007/978-3-030-12734-3_9.

10. Adams GE. Chemical radiosensitization of hypoxic cells. Br Med Bull. 1973 Jan;29(1):48-53. doi: 10.1093/oxfordjournals.bmb.a070956.

11. Proverbs-Singh T, Feldman JL, Morris MJ, Autio KA, Traina TA. Targeting the androgen receptor in prostate and breast cancer: several new agents in development. Endocr Relat Cancer. 2015 Jun;22(3):R87-R106. doi: 10.1530/ERC-14-0543.

12. Michmerhuizen AR, Chandler B, Olsen E, Wilder-Romans K, Moubadder L, Liu M, et al. C. Seviteronel, a Novel CYP17 Lyase Inhibitor and Androgen Receptor Antagonist, Radiosensitizes AR-Positive Triple Negative Breast Cancer Cells. Front Endocrinol (Lausanne). 2020 Feb 11;11:35. doi: 10.3389/fendo.2020.00035.

13. Kang HC, Chie EK, Kim HJ, Kim JH, Kim IH, Kim K, et al. A phthalimidoalkanamide derived novel DNMT inhibitor enhanced radiosensitivity of A549 cells by inhibition of homologous recombination of DNA damage. Invest New Drugs. 2019 Dec;37(6):1158-1165. doi: 10.1007/s10637-019-00730-6.

14. Laird JH, Lok BH, Ma J, Bell A, de Stanchina E, Poirier JT, Rudin CM. Talazoparib Is a Potent Radiosensitizer in Small Cell Lung Cancer Cell Lines and Xenografts. Clin Cancer Res. 2018 Oct 15;24(20):5143-5152. doi: 10.1158/1078-0432.CCR-18-0401.

15. Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. Nat Rev Cancer. 2008 Mar;8(3):193-204. doi: 10.1038/nrc2342.
16. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature. 2012 Jan 18;481(7381):287-94. doi: 10.1038/nature10760.
17. Ray Chaudhuri A, Hashimoto Y, Herrador R, Neelsen KJ, Fachinetti D, Bermejo R, et al. M. Topoisomerase I poisoning results in PARP-mediated replication fork reversal. Nat Struct Mol Biol. 2012 Mar 4;19(4):417-23. doi: 10.1038/nsmb.2258.
18. Hastak K, Bhutra S, Parry R, Ford JM. Poly (ADP-ribose) polymerase inhibitor, an effective radiosensitizer in lung and pancreatic cancers. Oncotarget. 2017 Apr 18;8(16):26344-26355. doi: 10.18632/oncotarget.15464.
19. Buckley AM, Dunne MR, Lynam-Lennon N, Kennedy SA, Cannon A, Reynolds AL, et al. Pyrazinib (P3), [(E)-2-(2-Pyrazin-2-yl-vinyl)-phenol], a small molecule pyrazine compound enhances radiosensitivity in oesophageal adenocarcinoma. Cancer Lett. 2019 Apr 10;447:115-129. doi: 10.1016/j.canlet.2019.01.009.
20. Tang Q, Wu L, Xu M, Yan D, Shao J, Yan S. Osalmid, a Novel Identified RRM2 Inhibitor, Enhances Radiosensitivity of Esophageal Cancer. Int J Radiat Oncol Biol Phys. 2020 Dec 1;108(5):1368-1379. doi: 10.1016/j.ijrobp.2020.07.2322.
21. Lian X, Zhu C, Lin H, Gao Z, Li G, Zhang N, et al. Radiosensitization of HER2-positive esophageal cancer cells by pyrotinib. Biosci Rep. 2020 Feb 28;40(2):BSR20194167. doi: 10.1042/BSR20194167.
22. Qian X, Tan C, Yang B, Wang F, Ge Y, Guan Z, Cai J. Astaxanthin increases radiosensitivity in esophageal squamous cell carcinoma through inducing apoptosis and G2/M arrest. Dis Esophagus. 2017 Jun 1;30(6):1-7. doi: 10.1093/dote/dox027.
23. Ding YQ, Zhu HC, Chen XC, Sun XC, Yang X, Qin Q, et al. Sunitinib modulates the radiosensitivity of esophageal squamous cell carcinoma cells in vitro. Dis Esophagus. 2016 Nov;29(8):1144-1151. doi: 10.1111/dote.12440.
24. Vann KR, Oviatt AA, Osheroff N. Topoisomerase II Poisons: Converting Essential Enzymes into Molecular Scissors. Biochemistry. 2021 Jun 1;60(21):1630-1641. doi: 10.1021/acs.biochem.1c00240.
25. Deweese JE, Osheroff N. The DNA cleavage reaction of topoisomerase II: wolf in sheep's clothing. Nucleic Acids Res. 2009 Feb;37(3):738-48. doi: 10.1093/nar/gkn937.
26. Pommier Y, Leo E, Zhang H, Marchand C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chem Biol. 2010 May 28;17(5):421-33. doi: 10.1016/j.chembiol.2010.04.012.
27. Pendleton M, Lindsey RH Jr, Felix CA, Grimwade D, Osheroff N. Topoisomerase II and leukemia. Ann N Y Acad Sci. 2014 Mar;1310(1):98-110. doi: 10.1111/nyas.12358.
28. Tang Q, Ma J, Sun J, Yang L, Yang F, Zhang W, Li R, et al. Genistein and AG1024 synergistically increase the radiosensitivity of prostate cancer cells. Oncol Rep. 2018 Aug;40(2):579-588. doi: 10.3892/or.2018.6468.
29. Skwarska A, Ramachandran S, Dobrynin G, Leszczynska KB, Hammond EM. The imidazoacridinone C-1311 induces p53-dependent senescence or p53-independent apoptosis and sensitizes cancer cells to radiation. Oncotarget. 2017 May 9;8(19):31187-31198. doi: 10.18632/oncotarget.16102.
30. Cammarota F, Conte A, Aversano A, Muto P, Ametrano G, Riccio P, et al. Lithium chloride increases sensitivity to photon irradiation treatment in primary mesenchymal colon cancer cells. Mol Med Rep. 2020 Mar;21(3):1501-1508. doi: 10.3892/mmr.2020.10956.
31. Pal I, Dey KK, Chaurasia M, Parida S, Das S, Rajesh Y, et al. Cooperative effect of BI-69A11 and celecoxib enhances radiosensitization by modulating DNA damage repair in colon carcinoma. Tumour Biol. 2016 May;37(5):6389-402. doi: 10.1007/s13277-015-4399-6.
32. Pascual-Serra R, Fernández-Aroca DM, Sabater S, Roche O, Andrés I, Ortega-Muelas M, et al. p38β (MAPK11) mediates gemcitabine-associated radiosensitivity in sarcoma experimental models. Radiother Oncol. 2021 Mar;156:136-144. doi: 10.1016/j.radonc.2020.12.008.
33. Waissi W, Nicol A, Jung M, Rousseau M, Jarnet D, Noel G, et al. Radiosensitizing Pancreatic Cancer with PARP Inhibitor and Gemcitabine: An In Vivo and a Whole-Transcriptome Analysis after Proton or Photon Irradiation. Cancers (Basel). 2021 Jan 30;13(3):527. doi: 10.3390/cancers13030527.
34. Vance S, Liu E, Zhao L, Parsels JD, Parsels LA, Brown JL, et al. Selective radiosensitization of p53 mutant pancreatic cancer cells by combined inhibition of Chk1 and PARP1. Cell Cycle. 2011 Dec 15;10(24):4321-9. doi: 10.4161/cc.10.24.18661.
35. Zhang Y, Zuo Y, Guan Z, Lu W, Xu Z, Zhang H, et al. Salinomycin radiosensitizes human nasopharyngeal carcinoma cell line CNE-2 to radiation. Tumour Biol. 2016 Jan;37(1):305-11. doi: 10.1007/s13277-015-3730-6.
36. Geng CX, Zeng ZC, Wang JY, Xuan SY, Lin CM. Docetaxel shows radiosensitization in human hepatocellular carcinoma cells. World J Gastroenterol. 2005 May 21;11(19):2990-3. doi: 10.3748/wjg.v11.i19.2990.
37. Lee IJ, Seong J. Radiosensitizers in hepatocellular carcinoma. Semin Radiat Oncol. 2011 Oct;21(4):303-11. doi: 10.1016/j.semradonc.2011.05.008.
38. Nath M, Mridula, Kumari R. Microwave-assisted synthesis of mixed ligands organotin(IV) complexes of 1,10-phenanthroline and l-proline: Physicochemical characterization, DFT calculations, chemotherapeutic potential validation by in vitro DNA binding and nuclease activity. J Photochem Photobiol B. 2017 Sep;174:182-194. doi: 10.1016/j.jphotobiol.2017.07.017.
39. Liu HM, Wu Q, Cao JQ, Wang X, Song Y, Mei WJ, Wang XC. A phenanthroline derivative enhances radiosensitivity of hepatocellular carcinoma cells by inducing mitochondria-dependent apoptosis. Eur J Pharmacol. 2019 Jan 15;843:285-291. doi: 10.1016/j.ejphar.2018.10.031.
40. Zhang XH, Cao MQ, Li XX, Zhang T. Apatinib as an alternative therapy for advanced hepatocellular carcinoma. World J Hepatol. 2020 Oct 27;12(10):766-774. doi: 10.4254/wjh.v12.i10.766.
41. Yang C, Qin S. Apatinib targets both tumor and endothelial cells in hepatocellular carcinoma. Cancer Med. 2018 Sep;7(9):4570-4583. doi: 10.1002/cam4.1664.
42. Zhang H, Cao Y, Chen Y, Li G, Yu H. Apatinib promotes apoptosis of the SMMC-7721 hepatocellular carcinoma cell line via the PI3K/Akt pathway. Oncol Lett. 2018 Apr;15(4):5739-5743. doi: 10.3892/ol.2018.8031.
43. Liao J, Jin H, Li S, Xu L, Peng Z, Wei G, et al. Apatinib potentiates irradiation effect via suppressing PI3K/AKT signaling pathway in hepatocellular carcinoma. J Exp Clin Cancer Res.

2019 Nov 6;38(1):454. doi: 10.1186/s13046-019-1419-1.
44. Göttgens EL, Bussink J, Leszczynska KB, Peters H, Span PN, Hammond EM. Inhibition of CDK4/CDK6 Enhances Radiosensitivity of HPV Negative Head and Neck Squamous Cell Carcinomas. Int J Radiat Oncol Biol Phys. 2019 Nov 1;105(3):548-558. doi: 10.1016/j.ijrobp.2019.06.2531.
45. Groselj B, Sharma NL, Hamdy FC, Kerr M, Kiltie AE. Histone deacetylase inhibitors as radiosensitisers: effects on DNA damage signalling and repair. Br J Cancer. 2013 Mar 5;108(4):748-54. doi: 10.1038/bjc.2013.21.
46. Tsai YC, Wang TY, Hsu CL, Lin WC, Chen JY, Li JH, et al. Selective inhibition of HDAC6 promotes bladder cancer radiosensitization and mitigates the radiation-induced CXCL1 signalling. Br J Cancer. 2023 May;128(9):1753-1764. doi: 10.1038/s41416-023-02195-0.
47. Paillas S, Then CK, Kilgas S, Ruan JL, Thompson J, Elliott A, Smart S, Kiltie AE. The Histone Deacetylase Inhibitor Romidepsin Spares Normal Tissues While Acting as an Effective Radiosensitizer in Bladder Tumors in Vivo. Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):212-221. doi: 10.1016/j.ijrobp.2020.01.015.
48. White E. Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer. 2012 Apr 26;12(6):401-10. doi: 10.1038/nrc3262.
49. Wei H, Wei S, Gan B, Peng X, Zou W, Guan JL. Suppression of autophagy by FIP200 deletion inhibits mammary tumorigenesis. Genes Dev. 2011 Jul 15;25(14):1510-27. doi: 10.1101/gad.2051011.
50. Schleicher SM, Moretti L, Varki V, Lu B. Progress in the unraveling of the endoplasmic reticulum stress/autophagy pathway and cancer: implications for future therapeutic approaches. Drug Resist Updat. 2010 Jun;13(3):79-86. doi: 10.1016/j.drup.2010.04.002.
51. Wang F, Tang J, Li P, Si S, Yu H, Yang X, et al. Chloroquine Enhances the Radiosensitivity of Bladder Cancer Cells by Inhibiting Autophagy and Activating Apoptosis. Cell Physiol Biochem. 2018;45(1):54-66. doi: 10.1159/000486222.
52. Liu Y, Zhang P, Li F, Jin X, Li J, Chen W, Li Q. Metal-based *NanoEnhancers* for Future Radiotherapy: Radiosensitizing and Synergistic Effects on Tumor Cells. Theranostics. 2018 Feb 12;8(7):1824-1849. doi: 10.7150/thno.22172.
53. Vines JB, Yoon JH, Ryu NE, Lim DJ, Park H. Gold Nanoparticles for Photothermal Cancer Therapy. Front Chem. 2019 Apr 5;7:167. doi: 10.3389/fchem.2019.00167.
54. Lu VM, McDonald KL, Townley HE. Realizing the therapeutic potential of rare earth elements in designing nanoparticles to target and treat glioblastoma. Nanomedicine (Lond). 2017 Oct;12(19):2389-2401. doi: 10.2217/nnm-2017-0193.
55. Kobayashi K, Usami N, Porcel E, Lacombe S, Le Sech C. Enhancement of radiation effect by heavy elements. Mutat Res. 2010 Apr-Jun;704(1-3):123-31. doi: 10.1016/j.mrrev.2010.01.002.
56. Stewart C, Konstantinov K, McKinnon S, Guatelli S, Lerch M, Rosenfeld A, et al. First proof of bismuth oxide nanoparticles as efficient radiosensitisers on highly radioresistant cancer cells. Phys Med. 2016 Nov;32(11):1444-1452. doi: 10.1016/j.ejmp.2016.10.015.
57. Saberi A, Shahbazi-Gahrouei D, Abbasian M, Fesharaki M, Baharlouei A, Arab-Bafrani Z. Gold nanoparticles in combination with megavoltage radiation energy increased radiosensitization and apoptosis in colon cancer HT-29 cells. Int J Radiat Biol. 2017 Mar;93(3):315-323. doi: 10.1080/09553002.2017.1242816.
58. Habiba K, Aziz K, Sanders K, Santiago CM, Mahadevan LSK, Makarov V, et al. Enhancing Colorectal Cancer Radiation Therapy Efficacy using Silver Nanoprisms Decorated with Graphene as Radiosensitizers. Sci Rep. 2019 Nov 19;9(1):17120. doi: 10.1038/s41598-019-53706-0.
59. Mirjolet C, Boudon J, Loiseau A, Chevrier S, Boidot R, Oudot A, et al. Docetaxel-titanate nanotubes enhance radiosensitivity in an androgen-independent prostate cancer model. Int J Nanomedicine. 2017 Aug 30;12:6357-6364. doi: 10.2147/IJN.S139167.
60. Lavanya V, Adil M, Ahmed N, Rishi AK, Jamal S. Small molecule inhibitors as emerging cancer therapeutics. Integr Cancer Sci Ther. 2014;1:39–46. doi: 10.15761/ICST.1000109.
61. Balakrishnan L, Bambara RA. Flap endonuclease 1. Annu Rev Biochem. 2013;82:119-38. doi: 10.1146/annurev-biochem-072511-122603.
62. Zheng L, Jia J, Finger LD, Guo Z, Zer C, Shen B. Functional regulation of FEN1 nuclease and its link to cancer. Nucleic Acids Res. 2011 Feb;39(3):781-94. doi: 10.1093/nar/gkq884.
63. Shen B, Singh P, Liu R, Qiu J, Zheng L, Finger LD, Alas S. Multiple but dissectible functions of FEN-1 nucleases in nucleic acid processing, genome stability and diseases. Bioessays. 2005 Jul;27(7):717-29. doi: 10.1002/bies.20255.
64. Liu S, Lu G, Ali S, Liu W, Zheng L, Dai H, et al. Okazaki fragment maturation involves α-segment error editing by the mammalian FEN1/MutSα functional complex. EMBO J. 2015 Jul 2;34(13):1829-43. doi: 10.15252/embj.201489865.
65. He L, Zhang Y, Sun H, Jiang F, Yang H, Wu H, et al. Targeting DNA Flap Endonuclease 1 to Impede Breast Cancer Progression. EBioMedicine. 2016 Dec;14:32-43. doi: 10.1016/j.ebiom.2016.11.012.
66. Zou J, Zhu L, Jiang X, Wang Y, Wang Y, Wang X, Chen B. Curcumin increases breast cancer cell sensitivity to cisplatin by decreasing FEN1 expression. Oncotarget. 2018 Jan 10;9(13):11268-11278. doi: 10.18632/oncotarget.24109.
67. Li JL, Wang JP, Chang H, Deng SM, Du JH, Wang XX, et al. FEN1 inhibitor increases sensitivity of radiotherapy in cervical cancer cells. Cancer Med. 2019 Dec;8(18):7774-7780. doi: 10.1002/cam4.2615.
68. Baek SJ, Ishii H, Tamari K, Hayashi K, Nishida N, Konno M, et al. Cancer stem cells: The potential of carbon ion beam radiation and new radiosensitizers (Review). Oncol Rep. 2015 Nov;34(5):2233-7. doi: 10.3892/or.2015.4236.
69. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2002 Nov 26;99(24):15524-9. doi: 10.1073/pnas.242606799.
70. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. Nature. 2005 Jun 9;435(7043):828-33. doi: 10.1038/nature03552.
71. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature. 2007 Oct 11;449(7163):682-8. doi: 10.1038/nature06174. Epub 2007 Sep 26. Erratum in: Nature. 2008 Sep 11;455(7210):256.

72. Zhang P, Wang L, Rodriguez-Aguayo C, Yuan Y, Debeb BG, Chen D, et al. miR-205 acts as a tumour radiosensitizer by targeting ZEB1 and Ubc13. Nat Commun. 2014 Dec 5;5:5671. doi: 10.1038/ncomms6671.
73. Huang F, Tang J, Zhuang X, Zhuang Y, Cheng W, Chen W, et al. MiR-196a promotes pancreatic cancer progression by targeting nuclear factor kappa-B-inhibitor alpha. PLoS One. 2014 Feb 4;9(2):e87897. doi: 10.1371/journal.pone.0087897.
74. Baek SJ, Sato K, Nishida N, Koseki J, Azuma R, Kawamoto K, et al. MicroRNA miR-374, a potential radiosensitizer for carbon ion beam radiotherapy. Oncol Rep. 2016 Nov;36(5):2946-2950. doi: 10.3892/or.2016.5122.
75. Qi T, Dong Y, Gao Z, Xu J. Research Progress on the Anti-Cancer Molecular Mechanisms of Huaier. Onco Targets Ther. 2020 Dec 8;13:12587-12599. doi: 10.2147/OTT.S281328.
76. Ding X, Yang Q, Kong X, Haffty BG, Gao S, Moran MS. Radiosensitization effect of Huaier on breast cancer cells. Oncol Rep. 2016 May;35(5):2843-50. doi: 10.3892/or.2016.4630.
77. Su YJ, Huang SY, Ni YH, Liao KF, Chiu SC. Anti-Tumor and Radiosensitization Effects of N-Butylidenephthalide on Human Breast Cancer Cells. Molecules. 2018 Jan 25;23(2):240. doi: 10.3390/molecules23020240.
78. Zhang D, Dong Y, Zhao Y, Zhou C, Qian Y, Hegde ML, et al. Sinomenine hydrochloride sensitizes cervical cancer cells to ionizing radiation by impairing DNA damage response. Oncol Rep. 2018 Nov;40(5):2886-2895. doi: 10.3892/or.2018.6693.
79. Zhang F, Fan B, Mao L. Radiosensitizing effects of Cyclocarya paliurus polysaccharide on hypoxic A549 and H520 human non-small cell lung carcinoma cells. Int J Mol Med. 2019 Oct;44(4):1233-1242. doi: 10.3892/ijmm.2019.4289.
80. Xie JH, Xie MY, Nie SP, Shen MY, Wang YX and Li C. Isolation, chemical composition and antioxidant activities of a water-soluble polysaccharide from Cyclocarya paliurus (Batal.) Iljinskaja. Food Chem. 2010;119:1626–1632.
81. Xie JH, Liu X, Shen MY, Nie SP, Zhang H, Li C, et al. Purification, physicochemical characterisation and anticancer activity of a polysaccharide from Cyclocarya paliurus leaves. Food Chem. 2013 Feb 15;136(3-4):1453-60. doi: 10.1016/j.foodchem.2012.09.078.
82. Li S, Li J, Guan XL, Li J, Deng SP, Li LQ, et al. Hypoglycemic effects and constituents of the barks of Cyclocarya paliurus and their inhibiting activities to glucosidase and glycogen phosphorylase. Fitoterapia. 2011 Oct;82(7):1081-5. doi: 10.1016/j.fitote.2011.07.002.
83. Sliva D. Medicinal mushroom Phellinus linteus as an alternative cancer therapy. Exp Ther Med. 2010 May;1(3):407-411. doi: 10.3892/etm_00000063.
84. Li YG, Ji DF, Zhong S, Liu PG, Lv ZQ, Zhu JX, et al. Polysaccharide from Phellinus linteus induces S-phase arrest in HepG2 cells by decreasing calreticulin expression and activating the P27kip1-cyclin A/D1/E-CDK2 pathway. J Ethnopharmacol. 2013 Oct 28;150(1):187-95. doi: 10.1016/j.jep.2013.08.028.
85. Zong A, Cao H, Wang F. Anticancer polysaccharides from natural resources: a review of recent research. Carbohydr Polym. 2012 Nov 6;90(4):1395-410. doi: 10.1016/j.carbpol.2012.07.026.
86. Park BJ, Lim YS, Lee HJ, Eum WS, Park J, Han KH, et al. Anti-oxidative effects of Phellinus linteus and red ginseng extracts on oxidative stress-induced DNA damage. BMB Rep. 2009 Aug 31;42(8):500-5. doi: 10.5483/bmbrep.2009.42.8.500.
87. Kim BC, Jeon WK, Hong HY, Jeon KB, Hahn JH, Kim YM, et al. The anti-inflammatory activity of Phellinus linteus (Berk. & M.A. Curt.) is mediated through the PKCdelta/Nrf2/ARE signaling to up-regulation of heme oxygenase-1. J Ethnopharmacol. 2007 Sep 5;113(2):240-7. doi: 10.1016/j.jep.2007.05.032.
88. Zhao C, Liao Z, Wu X, Liu Y, Liu X, Lin Z, Huang Y, Liu B. Isolation, purification, and structural features of a polysaccharide from Phellinus linteus and its hypoglycemic effect in alloxan-induced diabetic mice. J Food Sci. 2014 May;79(5):H1002-10. doi: 10.1111/1750-3841.12464.
89. Wang H, Wu G, Park HJ, Jiang PP, Sit WH, van Griensven LJ, Wan JM. Protective effect of Phellinus linteus polysaccharide extracts against thioacetamide-induced liver fibrosis in rats: a proteomics analysis. Chin Med. 2012 Oct 18;7(1):23. doi: 10.1186/1749-8546-7-23.
90. Jeong YK, Oh JY, Yoo JK, Lim SH, Kim EH. The Biofunctional Effects of Mesima as a Radiosensitizer for Hepatocellular Carcinoma. Int J Mol Sci. 2020 Jan 29;21(3):871. doi: 10.3390/ijms21030871.
91. Yan Y, Su W, Zeng S, Qian L, Chen X, Wei J, et al. Effect and Mechanism of Tanshinone I on the Radiosensitivity of Lung Cancer Cells. Mol Pharm. 2018 Nov 5;15(11):4843-4853. doi: 10.1021/acs.molpharmaceut.8b00489.
92. Kuo WT, Tsai YC, Wu HC, Ho YJ, Chen YS, Yao CH, Yao CH. Radiosensitization of non-small cell lung cancer by kaempferol. Oncol Rep. 2015 Nov;34(5):2351-6. doi: 10.3892/or.2015.4204.
93. Mundi PS, Sachdev J, McCourt C, Kalinsky K. AKT in cancer: new molecular insights and advances in drug development. Br J Clin Pharmacol. 2016 Oct;82(4):943-56. doi: 10.1111/bcp.13021.
94. Mayer IA, Arteaga CL. The PI3K/AKT Pathway as a Target for Cancer Treatment. Annu Rev Med. 2016;67:11-28. doi: 10.1146/annurev-med-062913-051343.
95. Xu Z, Yan Y, Xiao L, Dai S, Zeng S, Qian L, et al. Radiosensitizing effect of diosmetin on radioresistant lung cancer cells via Akt signaling pathway. PLoS One. 2017 Apr 17;12(4):e0175977. doi: 10.1371/journal.pone.0175977.
96. Stritzelberger J, Lainer J, Gollwitzer S, Graf W, Jost T, Lang JD, Mueller TM, Schwab S, Fietkau R, Hamer HM, Distel L. Ex vivo radiosensitivity is increased in non-cancer patients taking valproate. BMC Neurol. 2020 Oct 24;20(1):390. doi: 10.1186/s12883-020-01966-z.
97. Zhou W, Guo Y, Zhang X, Jiang Z. Lys05 induces lysosomal membrane permeabilization and increases radiosensitivity in glioblastoma. J Cell Biochem. 2020 Feb;121(2):2027-2037. doi: 10.1002/jcb.29437.
98. Neckers L. Heat shock protein 90: the cancer chaperone. J Biosci. 2007 Apr;32(3):517-30. doi: 10.1007/s12038-007-0051-y.
99. Mahalingam D, Swords R, Carew JS, Nawrocki ST, Bhalla K, Giles FJ. Targeting HSP90 for cancer therapy. Br J Cancer. 2009 May 19;100(10):1523-9. doi: 10.1038/sj.bjc.6605066.
100. Bull EE, Dote H, Brady KJ, Burgan WE, Carter DJ, Cerra MA, Oswald KA, Hollingshead MG, Camphausen K, Tofilon PJ. Enhanced tumor cell radiosensitivity and abrogation of G2 and S phase arrest by the Hsp90 inhibitor

17-(dimethylaminoethylamino)-17-demethoxygeldanamycin. Clin Cancer Res. 2004 Dec 1;10(23):8077-84. doi: 10.1158/1078-0432.CCR-04-1212.
101. Dote H, Burgan WE, Camphausen K, Tofilon PJ. Inhibition of hsp90 compromises the DNA damage response to radiation. Cancer Res. 2006 Sep 15;66(18):9211-20. doi: 10.1158/0008-5472.CAN-06-2181.
102. Stingl L, Stühmer T, Chatterjee M, Jensen MR, Flentje M, Djuzenova CS. Novel HSP90 inhibitors, NVP-AUY922 and NVP-BEP800, radiosensitise tumour cells through cell-cycle impairment, increased DNA damage and repair protraction. Br J Cancer. 2010 May 25;102(11):1578-91. doi: 10.1038/sj.bjc.6605683.
103. Djuzenova CS, Blassl C, Roloff K, Kuger S, Katzer A, Niewidok N, et al. Hsp90 inhibitor NVP-AUY922 enhances radiation sensitivity of tumor cell lines under hypoxia. Cancer Biol Ther. 2012 Apr;13(6):425-34. doi: 10.4161/cbt.19294.
104. Kudryavtsev VA, Khokhlova AV, Mosina VA, Selivanova EI, Kabakov AE. Induction of Hsp70 in tumor cells treated with inhibitors of the Hsp90 activity: A predictive marker and promising target for radiosensitization. PLoS One. 2017 Mar 14;12(3):e0173640. doi: 10.1371/journal.pone.0173640.
105. Zhao M, Gu L, Li Y, Chen S, You J, Fan L, Wang Y, Zhao L. Chitooligosaccharides display anti-tumor effects against human cervical cancer cells via the apoptotic and autophagic pathways. Carbohydr Polym. 2019 Nov 15;224:115171. doi: 10.1016/j.carbpol.2019.115171.
106. Kim EK, Je JY, Lee SJ, Kim YS, Hwang JW, Sung SH, Moon SH, Jeon BT, Kim SK, Jeon YJ, Park PJ. Chitooligosaccharides induce apoptosis in human myeloid leukemia HL-60 cells. Bioorg Med Chem Lett. 2012 Oct 1;22(19):6136-8. doi: 10.1016/j.bmcl.2012.08.030.
107. Luo Z, Dong X, Ke Q, Duan Q, Shen L. Downregulation of CD147 by chitooligosaccharide inhibits MMP-2 expression and suppresses the metastatic potential of human gastric cancer. Oncol Lett. 2014 Jul;8(1):361-366. doi: 10.3892/ol.2014.2115.
108. Vo TS, Ngo DH, Kim SK. Gallic acid-grafted chitooligosaccharides suppress antigen-induced allergic reactions in RBL-2H3 mast cells. Eur J Pharm Sci. 2012 Sep 29;47(2):527-33. doi: 10.1016/j.ejps.2012.07.010.
109. Han FS, Yang SJ, Lin MB, Chen YQ, Yang P, Xu JM. Chitooligosaccharides promote radiosensitivity in colon cancer line SW480. World J Gastroenterol. 2016 Jun 14;22(22):5193-200. doi: 10.3748/wjg.v22.i22.5193.
110. Liu Q, Wang M, Kern AM, Khaled S, Han J, Yeap BY, Hong TS, Settleman J, Benes CH, Held KD, Efstathiou JA, Willers H. Adapting a drug screening platform to discover associations of molecular targeted radiosensitizers with genomic biomarkers. Mol Cancer Res. 2015 Apr;13(4):713-20. doi: 10.1158/1541-7786.MCR-14-0570.
111.Storch K, Cordes N. The impact of CDK9 on radiosensitivity, DNA damage repair and cell cycling of HNSCC cancer cells. Int J Oncol. 2016 Jan;48(1):191-8. doi: 10.3892/ijo.2015.3246.
112. Xu T, Ma M, Chi Z, Si L, Sheng X, Cui C, Dai J, Yu S, Yan J, Yu H, Wu X, Tang H, Yu J, Kong Y, Guo J. High G2 and S-phase expressed 1 expression promotes acral melanoma progression and correlates with poor clinical prognosis. Cancer Sci. 2018 Jun;109(6):1787-1798. doi: 10.1111/cas.13607.
113. Lei X, Du L, Zhang P, Ma N, Liang Y, Han Y, Qu B. Knockdown GTSE1 enhances radiosensitivity in non-small-cell lung cancer through DNA damage repair pathway. J Cell Mol Med. 2020 May;24(9):5162-5167. doi: 10.1111/jcmm.15165.