Review Article

Review of Natural Radiosensitizer in Radiotherapy for Cancer Treatment

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Received: 06-03-2025; **Revised:** 23-05-2025; **Accepted:** 10-06-2025; **Published online:** 15-06-2025.

ABSTRACT

The primary goal of conventional cancer treatment is to remove the tumor surgically, then administer chemotherapy or radiation therapy. The only treatments available to patients when surgery is not an option are radiation and, less frequently, chemotherapy. However, irradiation (alone or in combination) does not always ensure treatment effectiveness, despite major advancements in our understanding the method and current procedures for radiation therapy. Cancer cells radio resistance is one of the primary causes. Cancer patients live longer when their cancer cells are more radiosensitive since this enhances the mechanisms that lead to their removal during radiation therapy. Synthetic radiosensitizers are frequently employed in clinical practice; however, attention has recently been drawn to the use of natural materials, or phytocompounds, as adjuvants in radiation therapy. Within this review paper, we exclusively address naturally occurring radiosensitizers that are presently undergoing clinical trials (resveratrol, curcumin, genistein, quercetin, and withaferin) and those whose effects on radiation sensitivity have been consistently validated by numerous independent investigations.

Keywords: Cancer, Radiotherapy, Radiosensitizers, Natural Radiosensitizers.

INTRODUCTION

Cancer, which is defined as "the uncontrolled growth and spread of unwanted cells" is a group of over 100 different diseases that can be infectious, age-related, environmental, genetic, or caused by abnormal cells growing out of control and spreading to an adjacent area. Typically, our bodies produce fresh cells as needed and replaces old ones that die. This method does not always go smoothly. Cells develop unnecessarily and never die at the appropriate times. These excess cells can create a growth known as a tumor. Tumors may be benign or malignant. Benign tumors are not cancerous, although malignant ones are. Malignant tumor cells have the ability to infect surrounding tissues. They can also separate and disseminate to other areas of the body. [1] The development of cancer, known as carcinogenesis, can be designed and defined in a variety of ways. Cancer development requires six fundamental properties: self-sufficiency, proliferation, insensitivity to antiproliferative signals, apoptosis evasion, unlimited replication potential, vasculature maintenance, and, for malignancy, tissue invasion and metastasis.[2]Cancer development can be divided into three phases: initiations, the promotion, and progression. During initiation, the "cancer cell" undergoes genomic changes such as point mutations, gene deletion and amplification, and chromosomal rearrangements that cause irreversible cellular changes. Tumor development is promoted by the survival and clonal expansion of these "initiated" cells.[3]

Types of Cancer: -

The primary forms of cancer are:

1) Carcinoma: - A prevalent kind of cancer called carcinoma develops in the skin, lungs, breasts, pancreas, and another cell and tissue wall organs and glands as well as the digestive and respiratory systems. It is described as, Basal cell carcinoma.

Squamous cell carcinoma.

Renal cell carcinoma.

Invasive ductal carcinoma, and Adenocarcinoma.

It can either spread to other parts of the body or remain in the same place where it started

2) Sarcoma: - Less than 1% of all solid malignant malignancies in adults and approximately 21% of all children's solid malignant cancers are sarcomas, tumors of presumed mesenchymal origin. Sarcomas are not a single malignancy; rather, they are a collection of malignancies. Soft tissue sarcomas frequently develop in the body's deep skin tissues, blood vessels, muscles, joints, fat, and nerves. Malignant bone tumors like osteosarcomas and Ewing's sarcomas, as their names suggest, can occur in any part of the body's bones, but they are also frequently seen in cartilage.[4]

3) Melanoma: - These cells, which are lowest layer dermis cells that generate melanin, or pigment, are impacted by melanoma, a type of cancer. The neural crest is the source of melanocytes, which express a range of signalling proteins and variables that promote migration and metastasis after malignant transformation. Although melanoma only makes up 1% of skin malignancies, it is responsible for more than eighty percent of skin cancer deaths. frequently found in the epidermis and infrequently found in the mouth, stomach, and eye.[5]

4) Lymphoma: - Immune system lymphocytes, which are found in the spleen, thymus, lymph nodes, and bone

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marrow, are the source of lymphoma, a kind of cancer. There are two primary forms of lymphoma: non-Hodgkin lymphoma and Hodgkin lymphoma

5) Leukaemia: - Leukaemia is the collective term for a variety of hematologic malignancies caused by the aberrant proliferation of growing leukocytes. The proliferation may be classified as myelocytic or lymphocytic, according to the cell of origin and the rate of development. Generally, chemotherapy is used to treat leukaemia, albeit this varies depending on the kind. A number of environmental and genetic risk factors for leukaemia development are known to exist.

CAUSES OF CANCER:

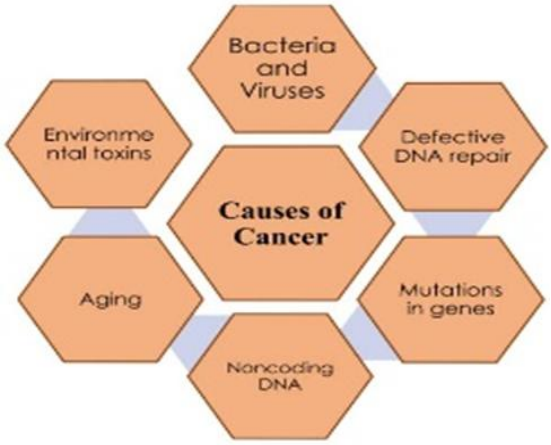

Figure 1

Symptoms: -

Numerous symptoms from the underlying disease and/or the disease's therapy may be experienced by cancer patients.

Table 1: Specific Symptoms by Cancer Type

Cancer type	Specific symptoms
Breast cancer	Lump in the breast, change in breast size or shape
Lung cancer	Coughing in blood, chest pain, shortness of breath
Colorectal cancer	Blood in stool, changes in bowel movements, abdominal pain
Prostate cancer	Starting or stopping urination, weak flow of urine, frequent urination
Gynecologic cancer	Abnormal vaginal bleeding, pelvic pain, stomach swelling

There has been extensive research on cancer symptoms and therapies.

1) Pain

2) Gastrointestinal symptoms (e.g., nausea, diarrhea)

3) Wasting/cachexia

4) Exhaustion

5) Cognitive deficits

6) Anxiety

7) Depression

8) Weakness

9) Sweating [6]

CANCER TREATMENT MODALITIES:

Cancer therapy modalities can be seen by classifying them into advanced, new, and modern categories in addition to conventional (traditional) ones. Nowadays, more than half of all ongoing clinical studies are focused on cancer treatments worldwide.7 factors, including the kind of cancer, where it is, and how severe it is, influence the choice of treatments and the course of the disease.

The most popular conventional therapy techniques

- Surgery
- Chemotherapy
- Radiotherapy

The most popular modern modalities include

- Hormone therapy
- Anti-angiogenic
- Stem cell therapies
- Immunotherapy
- Dendritic cell-based immunotherapy [7]

1) Surgical technique: -

Among the most effective and widely used therapies for both benign and malignant tumors, surgery, resection, or operation is regarded as having the lowest potential for tissue harm when compared to chemotherapy and radiation therapy. The fact that surgery can remove the tumor without needlessly damaging surrounding tissue is another factor supporting it as the best course of treatment. Various open or minimally invasive surgical techniques. When open surgery is performed, a single, wide incision is made, and the cancerous growth is typically removed along with a portion of good tissue connected to a few nearby lymph nodes. During minimally invasive surgery, on the other hand, the surgeon makes several little incisions rather than one large one, and then uses a laparoscope a thin tube with a camera attached to inspect the growth. Up close. The image is displayed on a screen by the camera. [8]

2) Chemotherapy techniques: -

Chemotherapy is the term for the use of chemicals to inhibit cancerous cells or the infectious agents of a disease, such as microorganisms, with little or no effect on the host cells. [9] Thus, chemotherapy for cancer and chemotherapy for microorganisms can be roughly classified into two categories. These medications differ from others in that their main goal is to either kill or suppress the target organism while having little to no effect on the host cell.

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Pharmaceuticals made synthetically as well as organically or by microbiological means must be included together. In conventional chemotherapy, every anticancer medication has a cytotoxic effect on both cancerous and healthy cells. Chemotherapy also kills bone marrow cells, hair follicle cells, and digestive tract cells all of which divide quickly under normal conditions. One of the most frequent adverse effects seen while receiving chemotherapy is: alopecia (hair loss), myelosuppression, and mucositis (inflammation of the digestive tract lining [10] Some strategies use medications termed photodynamic treatment or photo chemotherapy, which only becomes a cytotoxic agent when exposed to light. [11]

3) Radiotherapy techniques: -

In the treatment of cancer, radiotherapy is a popular and efficient method. Radiation is a physical agent that is used to destroy cancer cells. The administered radiation is referred to as irradiation because it causes energy to be deposited in the tissues' cells. and generates ions, which are electrically charged particles. This power has the potential to kill malignant cells directly or induce mutations that destroy cancer cells.[12]

4) Immunotherapy techniques:

Other treatment approach to the fight against cancer is immunotherapy. Generally speaking, immunotherapy refers to medical interventions that either stimulate or inhibit the immune system in order to combat cancer. Either the broad immune responses or the targeted immune system activation against the cancer cells is the goal. Immunotherapies that target various types of cancer.[13]

5) Anti- angiogenic techniques: -

Antiangiogenic therapy for cancer patients originated from observations made about forty-five years ago by Judah Folk man. He discovered that cancer cells need blood flow to develop larger than 1-2 mm3, which is why they trigger the angiogenesis process, which results in the formation of new blood vessels. Antiangiogenic therapy was proposed as a means of suppressing cancer development by inhibiting the production of tumor vessels, based on these data. [14] These drugs are being used to treat a variety of cancers, among lung, stomach, colorectal, hepatocellular, and breast cancer. [15]

6) Stem cells therapies: -

All methods using stem cells are considered therapy with stem cells, which is a potential novel strategy in the quest against cancer. Its enhanced ability to target cancer cells may reduce off target events and boost the therapeutic effectiveness of other medications. Preclinical trials are currently examining a variety of stem cell-based strategies, which provide both enormous promise and challenges for cancer treatment.

Stem cell types used to treat cancer.

1) Stem cells with pluripotency (PSCs)

2) Stem cells in adults (ASCs)

3) Stem cells for cancer (CSCs) [16]

RADIOTHERAPY:

High radiation dosages are used in radiotherapy (RT), a cancer treatment, to destroy cancer cells and reduce tumor size. To destroy cancer cells, radiation is one physiological agent that is used. Ionizing radiation is so named because it produces ions and other substances or particles with electrical charges, and deposits energy in the living tissues of the tissues it passes through. Cancer cells can be destroyed by this implanted energy, or their genetic composition can be changed. With variable degrees of success, radiation treatment is used to treat about 50% of cancer patients. The sensitivity of the surrounding normal tissues controls the maximum dose of ionizing radiation that can be applied to the cancer cells. [17] Victor Despeignes reported the first successful therapeutic anticancer use of radiotherapy in 1896, involving a patient suffering from stomach cancer. DNA, or deoxyribonucleic acid, is the genetic material of cells. Damage from high-energy radiation prevents cells from dividing and proliferating further. Differential cancer cell death results from cancer cells generally being less effective than healthy cells at repairing the damage done by radiation therapy. [18]

Why it's done: Almost every kind of cancer is treated with this method, it is a part of the treatment for over half of all cancer patients. This kind of diseases that are not malignant can also be treated with radiation treatment. Among these are benign tumors, or tumors that are not cancerous. Cancer cells are vulnerable to radiation because, unlike normal cells, which can quickly repair double strand breaks, cancer cells typically have weaker DNA repair mechanisms. Because of this, a fractionated approach—that is, dividing the entire radiation dose over a number of daily treatments—is usually employed. In this way, Normal cells' DNA damage is repaired throughout treatments, whereas cancer cells' damage accumulates over time and eventually becomes preferentially lethal. Responses in tumor and normal tissue are influenced by both the dose per fraction and the total dose. Generally speaking, radiation doses that are smaller on a daily basis are less likely to be hazardous; nevertheless, only some cell types vulnerable to these small daily doses. Consequently, it's necessary to strike a balance byAs a result, daily dosages that are both High amount of power to kill cancer cells and low enough to preserve healthy tissue must be balanced. A daily dose of 180–200 cGy is utilized for various types of cancer. Radiation is investigating a growing range of uses and techniques that will increase tolerability and accuracy due to the rapid advancement of technology. Despite the quick development of technology, the fundamentals of this field haven't altered in more than a century. Since the introduction of x-rays and their effect on cancer, radiation therapy has sought to enhance tumor regulation while preventing discomfort with the goal to give cancer patients with a good quality of life in addition to a cure. [18]

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How does radiation therapy work against the cancer cell?

The linear energy transfer (LET), total dosage, fractionation rate, and radiosensitivity of the targeted cells or tissues all affect how biologically effective (cell-killing) radiation is. High LET radiation deposits more energy on the targeted locations than low LET radiation, which deposits comparatively less energy. Even while the goal of radiation therapy is to destroy the tumor cell, radiation will inevitably harm the normal, noncancerous tissues that surround the tumor as well. On the other hand, radiation therapy aims to minimize the contact with healthy normal cells and maximize the dose to tumor cells. [19]

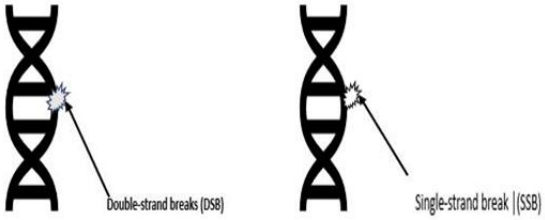

Figure 2

DNA is the biological target of radiation in cells: Figure 1: The DNA of the cell is the biological target of radiation. Cancer cells may die if their DNA sustains significant damage. More often than not, radiation therapy causes DNA double-strand breaks (DSBs), which can kill a cell or compromise its genome stability. In fact, a single DSB is typically sufficient to cause this kind of damage. Unrepairable double strand breaks in DNA are more responsible for single strand breaks, while the bulk of cancer cells die and surround healthy cells.

1) **Direct effects:** The direct contact of radiation with biological DNA might result in damage.

(Figure 2A)

2) **Indirect effects:** Ionization or activation of the cells' water component results in indirect

(Figure 2B)

2A 2B

Figure 3: Irradiation affects cellular DNA either directly or indirectly.

Radiation therapy and cell death: Using a variety of methods, radiation treatment can destroy cancer cells. Removing the cancer cells' ability to proliferate and ultimately causing their death is the primary objective of radiation therapy. Damaged DNA causes cancer cells to stop multiplying and ultimately dying.

Types and characteristics of cell death:

Radioactive treatment, like most anticancer therapies, operates by killing cells in several ways. Cancer cells are not instantly destroyed by radiation therapy. Before cancer cells begin to die, treatment may last for hours, days, or weeks. Once radiation therapy is finished, cancer cells may continue to die for several weeks or months. [20]

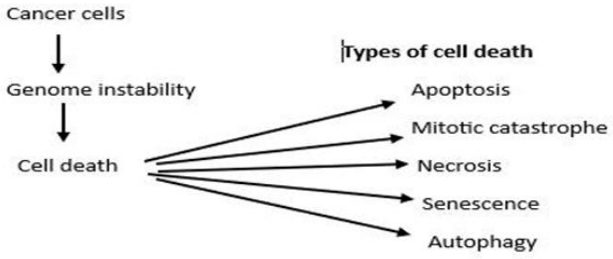

Figure 4: Several forms of radiation-induced cell death, Cells are mostly killed by irradiation by mitotic failure or death.

Types of radiation therapy:

Radiation therapy can be delivered two ways- Externally and internally.

1. External beam radiation therapy delivers radiation using a linear accelerator.

1) Specialized method external beam radiation therapy

- Three-dimensional conformal radiation therapy (3D-CRT)
- Intensity modulated radiation therapy (IMRT)
- Proton beam therapy
- Neutron beam therapy
- Stereotactic radiotherapy
- Image Guided radiation therapy
- Photo dynamic therapy [21]

2) Internal radiation therapy:

Internal radiation therapy, called brachytherapy or seed implants, involves placing radioactive sources inside the patient: Brachytherapy, another name is a medical procedure in which a radiation source is inserted within the patient. The majority of radionuclides utilized in brachytherapy release beta particles, which have a limited ability to penetrate tissue. During their demise, a few also release alpha particles and auger electrons, while a few more release gamma and X-rays. There is little chance of neighbouring normal tissues being harmed because the radiation only goes a short distance. The majority of internal radiation treatments target specific tissues or lesions by binding to them through molecular targets such metabolic pathways, ligand-receptors, or particular antibodies to the target antigen [22]

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Table 2: The benefits and drawbacks of various external beam radiation therapy (EBRT) technique types

External Beam Radiation therapy (EBRT) Technology	Types Of Cancer Treated	Benefits	Drawback
3-dimensional conformal radiotherapy (3DCRT)	Brain tumors, lung cancer, gastrointestinal (GI), breast cancer, and reproductive cancers.	Enhance the immediate response rate, decrease dryness of the mouth, minimize damage to the salivary glands, and enhance the overall outlook for patients diagnosed with nasopharyngeal carcinomas.	Shows increased gastrointestinal toxicity in endometrial cancer patients.
Intensity modulated radiotherapy (IMRT)	Cancers of the brain, gynecology, prostate, breast, lung, head and neck, and GL	Supply accurate & precise measurements.	Higher dose conformity indices make IMRT more susceptible to geometrical mistakes.
Volumetric modulated arc therapy (VMAT)	Head and neck, nonsmall cell lung cancer (NSCLC), prostate, gastrointestinal, gynecological, thoracic, central nervous system, and breast tumors	The apparatus offers a full 360° of irradiation directions and a full dosage quantity in a single change. Comparing VMAT treatment to IMRT, the former exhibits higher uniformity	An increase in low-level radiation exposure to the organs and tissues around it, with a higher probability of secondary cancers
Image guided radiotherapy (IGRT)	Prostate, lung and head and neck cancers	Considerable decrease in setup margins leading to decreased toxins in locations with observable, measurable, and inter- intra-fraction motion.	throughout daily imaging, including image quality, prolonged collection times
Stereotactic body radiation therapy (SBRT)	Prostate, head and neck, spinal, renal, pancreatic	The gadget lowers the potential of after complications and death by directly delivering high radiation doses to the tumor.	Adverse effects following treatment

Side effects: side effects of radiation therapy in normal tissue can be classified as either early (or acute) or late: Prior to, during, or shortly after (within weeks) radiation therapy treatment, early (or acute) side effects might happen. When the dose is restricted and tissue turnover is rapid, as in the case of the gut and oral mucosa, the early adverse effects are frequently reversible; in other cases, they are partially reversible and affect the skin, brain, and lungs (pneumonitis), causing weakness and memory loss. Late side effects are typically chronic and frequently worsen with time, which lowers patients' post-treatment quality of life. As a result, these are frequently used to establish radiation exposure limits. The time to reaction of late-responding tissues is dose-dependent and influenced by processes such cellular senescence, persistent inflammation, hypoxia, and fibrosis, in contrast to early side effects. The tissue's ability to regenerate itself is subsequently inhibited by each of these reactions. Crucially, fibrosis has a role in the pathophysiology of adverse consequences in the majority of tissues, including the liver, heart, and lungs. [23]

RADIOSENSITIZERS:

Radiosensitizers are substances that, when added to radiation, produce a higher degree of deactivation of tumors compared to what would be expected based on the combined effects of each method solo. It should come that Radiosensitizers will be an effective means of enhancing radiotherapy. They should be able to both pharmacologically reduce normal tissue damage and increase the radiosensitivity of malignant tissue.[24] Divided radiosensitizers into five groups: a) inhibiting intracellular other naturally present radioprotective substances; b) forming cytotoxic substances through the radioactive decay of the radiosensitizers; c) preventing biomolecule repair; d)

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thymine analogues that can integrate into chromosomal and (e) oxygen mimics with electrophilic activity. [25] This categorization paved the path for early-stage radiosensitizers by considering the degradation and repair processes of DNA. But as technology advances, an increasing number of substances and medications that exhibit radiation sensitization have come to be known as Radiosensitizers. Furthermore, a few comprehensive processes for radio sensitization have also been found. [26] The most recent research indicates that divided into three groups structural similarities: small molecules, macromolecules, and nanomaterials. The applications, primary function, and influencing aspects of these three radiosensitizers types— particularly those that are presently undergoing clinical trials—are outlined in the section that follows. Secondly, a synopsis of the radiosensitizers mechanism of action and development state is provided. Third, a presentation was made regarding the radio-sensitizer's potential development and use. [27]

Natural radiosensitizers: Even though numerous synthetic RS with various mechanisms have been created and studied, their therapeutic application can be limited by related toxicities. Long employed as chemo preventive agents, natural substances are currently being testing as new RS. Moreover, they are currently recognized in many cancers for their usage as biological guardians of the normal tissues, radiosensitizers, and antioxidants with pro-immune actions and safety profile. [28] In addition to having higher adverse effects, synthetic inhibitors only slightly improve treatment. It is necessary to develop more and new radiosensitizers in order to overcome such limitations. Foods naturally contain radiosensitizers, which are thought to be safer than synthetic ones. Additionally, natural goods have better benefits as biological and radiation helps for normal cells due to their immune-boosting and antioxidant qualities. Among the few naturally occurring radiation sensitizers are quercetin, genistein, and curcumin, Resveratrol, withaferin A. Their impact and function in cancer treatment as a radioprotector. [29]

NATURAL RADIOSENSITIZERS:

1) Curcumin:

Figure 5

Scientific classification

Kingdom: plantae

Species: curcuma longa

Family: zingiberaceae

Order: zingiberales

Curcumin, also known as diferruloylmethane Turmeric, the primary component of curries, is a polyphenol known as -1,6 heptadiene-3,5-dione, which is found naturally in the zingiberaceae plant Curcuma longa. Because of its clear yellow colour, and it is frequently utilized as an ingredient in food (E100). Turmeric, or the rhizome of the ginger family plant, produces curcumin, a naturally occurring polyphenolic chemical. This plant is mostly cultivated in Asia countries. Curcumin has long been utilized as a natural remedy in traditional Chinese medicine because of its broad spectrum of biological activity, antiinflammatory, and antioxidant qualities. [30] The pharmacological properties of curcumin have been the subject of numerous investigations over the past 20 years; in particular, its anticancer properties are now well known. Numerous malignancies, including those of the colon, breast, head and neck, lung, and prostate, have been shown to be resistant to it. Protumoral activity have been found, fortunately [31]

Radiosensitizers of curcumin: Curcumin is one of the radiosensitizing compounds that has been investigated the most. Curcumin's anti-cancer effects have been investigated in several cancer types, and the majority of findings related to radio sensitization originate from laboratory experiments. [32] Through a variety of well-defined mechanisms, curcumin can radiosensitizer cells. EGFR (epidermal growth factor) and TGF-β (transforming growth factor-κ) are two examples of growth factors and RAS-associated proteins whose activity has been shown to be altered by ionizing radiation. [33]

Curcumin as a Radiosensitizers in Various Malignant:

1) Lung cancer: Among the most frequent cancers in men, lung cancer ranks third in women's cancer incidence. curcumin acts on the Wnt/β-catenin-dependent pathway, demonstrating its therapeutic promise in the treatment of lung cancer. In the same cell line, curcumin also inhibits the production of NF-κB and vascular endothelial growth factor (VEGF0). [34]Through enhanced apoptosis, G2/M arrest, and reduction of cell growth, has demonstrated cytotoxicity against non-small-cell lung cancer (NSCLC). Moreover, curcumin produces ROS, which triggers the DNA damage signalling pathway. [35] The low-dose given over an extended period of time on NSCLC cells were examined in a recent study. The cancer cells' ability to invade new locations and spread was significantly inhibited by curcumin doses ranging from 0.25 to 0.5 µM. [36]

2) Breast Cancer: This are remains the almost popular cancer type various women globally. A common pathway shared by several cancer cell types inside a single tumour is the focus of the drugs used in the present clinical strategy. Notch, human epidermal growth factor receptor 2 (Her-2), NF-κB, and signal transducer and activator of transcription 3 (STAT-3) are among the typical pathways that are targeted by different therapeutic strategies for breast cancer. It was shown that curcumin inhibited the phosphorylation of Akt,

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mTOR, and their downstream proteins, which caused several cancerous breast cell types, including T47D and MCF7, to cycle arrest. [37]

2) Genistein:

Figure 6: Genistein

Scientific classification

Kingdom: organic compounds

Family: Leguminosae

Species: Genistein

Source: soybeans and other legumes

Genistein as radiosensitizers:

A soy isoflavone called genistein reduces cell division and thereby increases apoptosis by blocking DNA topoisomerase II and tyrosine protein kinases. Additionally, these compounds have anti-angiogenic and anticancer effects by promoting the DNA repair pathway. [38] Numerous research investigations have shown that genistein suppresses the rise of multiple abnormal cell in vitro, like neuroblastoma, dermal malignancy, lymphoma, and prostate and breast cancer cells.[39]Consequently, the use of genistein was recommended to lower the ionizing radiation treatment dosage and the potential side effects associated with radiation therapy. [40]

Genistein as a Radiosensitizers in Various Malignant:

1) Breast Cancer: The radio sensitizing impact Effects genistein on different ER (estrogen receptor) status the disease cells were examined in a study. The epithelial human carcinoma cell lines MDA-MB-231 and MCF-7 were made public. to X-ray radiation (4 Gy) and genistein (5– 20 µM) treatments. The experimental results demonstrated increased DNA damage, cell cycle arrest at the G2/M phase due to up-regulated ATM, Chk2, Cdc25c, and Cdc2 phosphorylation, and increased sensitivity via a mitochondria-mediated apoptotic route. [41]

2) Lung cancer: The effects of genistein on radiosensitization were examined in both normal lung fibroblast cells and (NSCLC) cells. After being exposed to X-rays (4 Gy) for 48 hours, cells were treated with 10 µM genistein. The experimental results demonstrated that genistein increased oxidative stress-induced cellular damage in the A549 cell line by reducing GSH, an antioxidant component, and improving ROS. [42]According to certain studies, this combination treatment of genistein with ionizing radiation caused a drop in the cytoplasmic levels of Bcl-x, a recognized anti-apoptotic factor linked to lung cancer patients' radio resistance. [43]summing up, the authors propose that genistein may have a radio sensitizing effect on NSCLC cells due to its capacity to control the degree of Bcl-x cytoplasmic expression and, therefore, apoptotic and autophagic processes. [44]

3) Cervical cancer: According to experimental results, the combination of γ-irradiations (4 Gy) and genistein (40 µmol/L) significantly inhibited the growth of cervical cancer cells (Hela) and rise sensitivity by down-regulating (a protein that inhibits apoptosis), which in turn inhibits caspase 9 and blocks the apoptotic pathway. [45] Compared to malignant tumours, which had high expression of this inhibitor, normal differentiated tissues produced nothing [46] Genistein to lower the potential side effects associated with RT and the IR therapeutic dose. Drawing from prior research demonstrating Genistein's capacity to prevent cervical carcinoma cell proliferation in vitro. [47] Further research showed that genistein functions as a Radiosensitizers to stop the cell cycle in G2/M, particularly in ME180 cells, and furthermore another cells. This results in a dose-dependent increase of Cytochrome c through a decrease in Mcl-1 and total AKT, indicating a potential role in the apoptotic pathway. [48]

3) Withaferin

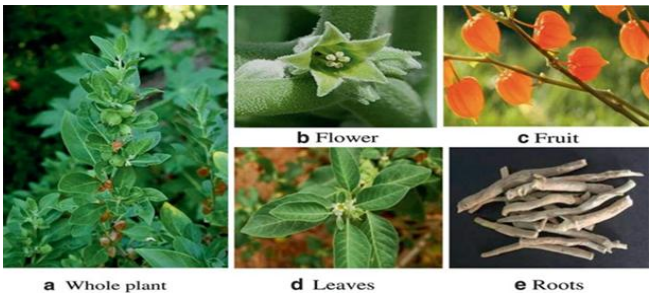

Figure 7: Withaferin

Scientific classification

Kingdom: organic compounds

Family: Solanaceae

Species: withaferin A

Sources: *Withania somnifera*

Withaferin as a Radiosensitizers: Steroid lactone Withaferin A (WA) part of a broad class of native to nature steroids learn as Withanolides. In the late 1950s, an A leaf extract from the Indian botanical Withania somnifera, commonly referred to as winter cherry or ashwagandha, was used to produce WA, the first withanolide to be isolated. [49] Has anti-tumour properties that have been documented, including as the suppression of angiogenesis, metastasis, and tumour cell proliferation. In the present investigation, we assessed the impact of Wit A on radiation-induced programmed cell kill in human kidney carcinoma, learn as Kaki cells. In contrast to Wit A or radiation alone, our data demonstrated a considerable increase in apoptosis caused by the

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combination of both, as evidenced by an increase in sub-G1 cell population and caspase-3 and PARP cleavage. Reactive oxygen species (ROS) production was also linked to an increase in radiation-induced apoptosis by Wit A. Apoptosis caused by radiation + Wit A decreased in Caki cells when Bcl-2 was expressed ectopically, and Wit A decreased the amounts of Bcl-2 protein. These findings collectively show that Wit A improved When considered collectively, these findings advise that Wit A produced more ROS, down-regulated Bcl-2, and phosphorylated Akt to increase radiation-induced apoptosis in Caki cells. Consequently, our research suggests that Wit A can be a useful Radiosensitizers in the treatment of cancer. [50]

Withaferin A Radiosensitizers in Various Malignant:

1) Lung cancer: Small cell lung cancer (15%) and non-small cell pulmonary cancer (NSCLC), which make up 85% of all cases of lung cancer, are the two primary forms of the disease. Additionally, this is categorized according to the driver oncogenic mutation, which includes p53 mutations (50%) and ALK (anaplastic lymphoma kinase) rearrangement (<5%), KRAS (20%), and EGFR (epidermal growth factor receptor) mutations (20%). [51] The authors have demonstrated that WFA, with IC50 values ranging from 0.3–1.49 µM, causes apoptotic cell death in both EGFR WT and mutant NSCLC cell lines. Additionally, WFA prevented H441 (EGFR WT and KRAS mutant c.35G > T) from growing in in vivo lung tumours in patients with NOD/SCID (non-obese diabetic/severe combination immune deficiency[52] WFA has been shown to use the annexin V/PI test to cause apoptosis in the NSCLC cell line A549 when used as a lung cancer treatment. Additionally, because treated cells had a higher proportion of G0/G1 phase cells, WFA decreased the growth of A549 cells. [53]

2) Breast Cancer: The phytochemical was discovered to downregulate the estrogen receptorα (ER-α) protein in MCF-7 cells when it was investigated for the proapoptotic response of WFA. The presence of 17β-estradiol reversed this effect. As a result, WFA has anti-estrogen properties, and its proapoptotic actions can be reduced by p53 knockdown. Apoptosis brought on by WFA's production of (ROS) is one of the several processes that has been widely studied [54]

3) Prostate cancer: A bioactive substance called withaferin A (WA) may be used to treat cancer, including prostate cancer. Oral withaferin dosage: 3-5 mg/kg A successfully stopped the growth prostate cancer cells by reducing the activation of Akt and increasing the activation of (FOXO3a)-mediated prostate apoptotic response. [55]

4) Quercetin

Scientific classification

Kingdom: organic compounds

Family: Asteraceae

Species: quercetin

Sources: fruits (apples, berries, grapes) vegetable, nuts

Figure 8: Quercetin

Quercetin as radiosensitizers: Quercetin (3, 30, 40, 5, 7 – five-flavonoids) is a flavonoid found in nature that is widely distributed in fruits and vegetables, including apples, almonds, berries, onions, cauliflower, and cabbage. It is also used in Chinese herbal medicine. [56] Quercetin has been demonstrated in studies to decrease UV radiation damages skin and increases white blood cells in human lymphocytes in the peripheral bloodstream and mice exposed to X-ray radiation. following irradiation or chemotherapy. [57] We suggested that the combination of radiation and quercetin would enhance tumour sensitivity due to the multifunctional properties of quercetin in the biological system. [58]

Quercetin as Radiosensitizers in Various Malignant:

1) Lung cancer by making (NSCLC) cells more radiosensitive, quercetin could help in the treatment of lung cancer with radiation therapy. In an effort to confirm the exact mechanism by which quercetin affects NSCLC cell radiosensitivity, GLC-82/R and HTB-182/R cells were transfected with miR-NC and miR-16-5p inhibitors, respectively, before being treated to 50 µM flavonoid for 48 hours. Quercetin clearly increased the expression of miR-16-5p in NSCLC cells, according to qRT-PCR, whereas miR-16-5p inhibitors significantly decreased the expression of miR-16-5p in NSCLC cells. MiR-16-5p inhibitors also lessened the impact of quercetin on apoptosis, colony survival, and NSCLC cell viability. Quercetin increased the expression of miR-16-5p, which in turn increased the sensitivity of NSCLC cells. [59]

2) Breast cancer: Quercetin has been investigated as an anti-tumoral chemical working against breast cancer (BC); however, because of the variability of the BC cell line genotypes employed, it is challenging to determine the doses and routes involved in its benefits. Early research on this type of cancer clearly showed quercetin's potential utility. Actually, quercetin at 7 µg/mL (or 23 µM) stopped cells in the G2/M phase when tested on the MDA-MB-468 cell line. [60]

3) Prostate cancer: Quercetin's power to stimulate apoptosis in different kinds of prostate has been extensively researched and is beginning to receive attention as the primary factor behind its anti-prostate cancer actions. Ultimately, it can be said that quercetin mostly causes prostate cancer to undergo apoptosis by controlling the ratios of Bcl-2, Bax, and Bcl-2; this is accomplished through

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the mitochondrial-mediated intrinsic pathway. Additionally, it can mediate the extrinsic pathway. [61]

5) Resveratrol

Figure 9: Resveratrol

Resveratrol Based on its numerous powerful biological activities and therapeutic qualities, resveratrol (3,40,5-trihydroxystilbene) is the most well-known and well-characterized derivative of stilbene. A multitude of information about the anticancer, cardioprotective, neuroprotective, antioxidant, and anti-inflammatory properties of resveratrol may be found in a number of outstanding review studies. It can be found in a variety of foods, such as peanuts, pomegranates, blueberries, soy beans, and grapes (Vitis vinifera). Resveratrol has a great deal of biological potential, but because of its poor bioavailability, its application in therapeutic treatments is currently restricted. In cancerous tissues, nanoparticles have enhanced RSV solubility, strength, kinetics, and biodistribution. [62]

Resveratrol as a Radiosensitizers:

Resveratrol's action, which makes cells more sensitive to ionizing radiation, is likely to go against the intended qualities of substances when considering the mechanisms that both support and restrict the efficacy of radiotherapy. However, resveratrol's impact on cells is consistent with the conventional idea of hormesis, which holds that an organism's response to a given substance depends on its dosage and whether it would be advantageous or detrimental.

Resveratrol has the ability to function in opposition to polyphenols' typical antioxidant properties when taken in an appropriately high amount. This is particularly significant when considering how ionizing radiation might sensitize cancerous cells, which can display various processes that increase their radiation resistance based on the type of cancer. [63]

Resveratrol as a Radiosensitizers in different malignant:

1) Lung cancer: The application of 20 µM drug also expand the inclination of non-small cell lung cancer cells to radiation doses from 0 to 8 Gy. This cooperative approach hastened the aging and death of cells by inducing radio sensitization through apoptosis-independent molecular pathways, increasing the generation of reactive oxygen species, and breaking DNA double strands. [64]

2) Breast Cancer: A breast cancer cell model was used to investigate the capacity to make cells more vulnerable to ionizing radiation. Combining resveratrol at different concentrations with radiation produced cytotoxic properties at dosages of 1, 2, and 3 Gy. The restricted cell growth, and inhibition of the cell cycle in the MCF-7 cell line. It's interesting to note that the optimal outcomes were obtained with 30 µM resveratrol and 3 Gy of radiation. [65]

3) Prostate cancer: An additional mechanism that makes prostate cancer cells more susceptible to ionizing radiation is the function of the proteins granzyme B and perforin, which are crucial components of lymphocyte and natural killer cell killing capabilities. [66] The researchers demonstrated that the cytotoxicity of a typical radiation therapy fraction (2 Gy) in PC cells was increased by resveratrol doses comparable to those found in human serum (2.5 and 5 µM), without causing any further harm to normal epithelial cells.

CONCLUSION

Natural radiosensitizers have demonstrated encouraging promise in raising radiation therapy's efficacy in the treatment of cancer. Information from studies conducted both in vitro and in vivo suggest that plant chemicals may be useful in raising cancer cells' sensitivity to radiation. However, there aren't many therapeutic uses for natural compounds in radiation therapy, which may be because of their limited body bioavailability. The mechanisms of action and clinical trials of natural radiosensitizers are covered in this article.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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