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Potential and Mechanism of Plants as Radioprotection Agents in Cancer Therapy: Review

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A B S T R A C T

Radiotherapy is a widely used treatment for cancer, yet it can cause harmful side effects due to oxidative stress and DNA damage in healthy tissues. This systematic literature review explores the potential of medical plants as natural radioprotective agents. Twenty plant species were identified, and their bioactive compounds such as flavonoids, polyphenols, saponins, and tannins were shown to exhibit antioxidant, anti-inflammatory, and DNA repair properties. The predominant mechanism of protection involves free radical scavenging. However, non-selective action and the possibility of protecting cancer cells remain major challenges. While in vivo and in vitro studies show promising results, further research is necessary to develop clinically applicable formulations. Natural plant-based agents offer a safer alternative to synthetic radioprotectors, potentially enhancing patient outcomes in radiotherapy.

Keywords: *Radioprotection; Antioxidants; Phytochemicals; Cancer therapy; Oxidative stress*

A B S T R A K

Radioterapi adalah metode pengobatan kanker yang umum digunakan, nemun memiliki efek samping akibat stress oksidatif dan kerusakan DNA pada jaringan sehat. Studi tinjauan literatur sistematis ini mengeksplorasi potensi tanaman obat sebagao agen radioprotektor alami. Sebanyak dua puluh spesies tanaman diidentifikasi, dan senyawa bioaktif di dalamnya seperti flavonoid, polifenol, saponin, dan tanin menunjukkan aktivitas antioksidan, antiinflamasi, dan perbaikan DNA. Mekanisme perlindungan utama adalah penangkapan radikal bebas. Namun, mekanisme yang tidak selektif dan potensi perlindungan terhadap sel kanker menjadi tantangan utama. Meskipun studi in vivo dan in vitro menunjukkan hasil yang menjanjikan, diperlukan penelitian lanjutan untuk mengembangkan formulasi yang dapat diterapkan secara klinis. Agen berbasis tanaman menawarkan alternatif yang lebih aman dibandingkan radioprotektor sintetis dan berpotensi meningkatkan hasil pengobatan radioterapi.

Kata kunci: Radioproteksi; Antioksidan; Fitokimia; Terapi kanker; Stres oksidatif

1. INTRODUCTION

Cancer is a serious threat to human life and health. Cancer is an abnormal cell that can grow and spread uncontrollably (Wardhani et al., 2022). According to data from the American Cancer Society, there were 19.3 million new cases of cancer worldwide in 2020. This number is projected to rise to 28.4 million new cases by 2040 (Sung et al., 2021). Cancer can be treated through surgery, chemotherapy, and radiotherapy. This medical treatment method uses ionizing radiation to eliminate cancer cells (Nurmansya & Miskiyah, 2021). Radiotherapy is a widely used and effective treatment for cancer, but it does come with potential side effects. The ionizing radiation used in radiotherapy targets cancer cells; however, it can also harm normal cells by generating free radicals and increasing oxidative stress. These effects can lead to a range of side effects, including inflammation, fibrosis, DNA damage, and an increased risk of developing secondary cancers (Wu et al., 2022). Efforts to protect healthy cells from damage caused by radiation exposure require further study.

Radioprotection is an approach aimed at minimizing the side effects of radiotherapy. Radiotherapy agents work by safeguarding normal cells from radiation damage through several mechanisms: they reduce the production of free radicals, enhance DNA repair processes, and modulate cellular responses to oxidative stress (Baatout, 2023). While synthetic agents like amifostine are used as radioprotectants, they often cause side effects, including nausea, hypotension, and allergic reactions (Masoud et al., 2023). The search for safer and more effective radioprotectors is essential.

Research into using natural materials as radioprotective agents is increasing annually. Medicinal plants have been utilized in traditional medicine for a long time, and these plants are known to contain various phytochemical compounds, such as flavonoids, polyphenols, saponins, and tannins. The phytochemical content in these plants has the potential to act as strong antioxidants, helping to reduce the negative effects caused by free radicals during radiotherapy (Issinger & Guerra, 2021). Natural antioxidants can help protect normal cells from oxidative damage caused by radiotherapy. Medicinal plants such as Curcuma longa, Ginkgo biloba, and Panax ginseng have the potential to serve as radioprotective agents. The bioactive compounds present in these plants work to reduce oxidative stress, protect DNA from damage, and enhance cell repair mechanisms (Turcov et al., 2023). Plant-based radioprotective agents offer a safer alternative for mitigating the side effects of radiotherapy.

This systematic literature review aims to explore current research on the potential of various plants as radioprotective agents in radiotherapy. The review will identify the types of plants that have been studied, the mechanisms of action of their bioactive compounds, and the effectiveness of these compounds in protecting healthy cells from the damage caused by radiotherapy.

2. METHOD

This study employs the Systematic Literature Review method, which is a structured approach used to collect, analyze, and synthesize various studies related to the potential and mechanisms of plants as radioprotective agents. The research process consists of several stages: formulating research questions, searching for relevant literature, determining inclusion and exclusion criteria, selecting the literature, presenting and processing the data, and drawing conclusions.

The first stage involves formulating research questions, specifically: What plants have the potential to serve as radioprotective agents? What mechanisms do these plants use to provide radioprotection in radiotherapy? In the second stage, a comprehensive literature search was conducted across various databases, including PubMed, MDPI, Taylor & Francis, Google Scholar, ScienceDirect, and Web of Science, to ensure broad coverage of relevant literature. The following keywords were used in the search: "radioprotection," "antioxidants," "cancer therapy," and "radiation protection by natural agents." This combination of keywords is used to gather relevant literature for study results. The selected articles include research published within the last five years (2019-2024) to ensure that the data is current and relevant. Additionally, only articles published in reputable scientific journals, conference proceedings, and textbooks related to the topic will be considered.

The inclusion criteria for the literature review comprised the following: research that evaluates the potential of plants or their bioactive compounds as radioprotective agents, studies that included in vitro and in vivo tests, and articles published in English or Indonesian within the last five years (2019-2024) to ensure the data's relevance and novelty. The exclusion criteria for this study included any articles that were not original research, those lacking full access, or those that only provided abstracts. Following this, the literature was selected based on these criteria, resulting in 20 relevant articles related to the keywords. The next step involved recording these articles in a table. The researcher then conducted an intensive review of the articles, focusing particularly on the results section. Finally, the researcher compared the findings from the various articles and drew conclusions from the systematic literature review.

3. RESULT AND DISCUSSION

After conducting a literature search on the specified database, several articles related to the potential and mechanisms of plants as radioprotective agents in radiotherapy were successfully identified. The results of the articles that met the inclusion and exclusion criteria are summarized in Table 1.

Table 1. Potential and mechanism of plants for radioprotection agent

No.	Plants	Types of radiation	Object	Mechanisms	Reference
1.	Alpina zerumbet (shell ginger)	UV radiation	Huma white blood cells	Free radical scavenging	(Ritwiz et al., 2019)
2.	Urtica dioica seeds (nettle seeds)	Photon radiation	Rats	Reduce oxidative stress	(Çakır et al., 2020)
3.	Inula racemosa root	Gamma radiation	Mice, Normal kidney epithelial (NKE) cell	Reduce oxidative stress	(Mohan & Gupta, 2019)
4.	Tragia involucrate (Indian nettle)	Gamma radiation	Human white blood cells	Free radical scavenging	(Thimmaiah et al., 2019)

5.	Dictyota dichotoma (brown algae)	x-ray radiation	Mice, Human melanoma cells	Free radical scavenging	(Malyarenko et al., 2019)
6.	Ecklonia cave (marine brown algae)	Gamma radiation	rat hepatosis cells	Free radical scavenging, reducing inflammation	(Sadeeshkumar et al., 2019)
7.	Vitis vinifera seeds (grape leaves)	Gamma radiation	mice	Antioxidant activity	(Targhi et al., 2019)
8.	Eloda canadensis (water grass), Salvia officinalis (sage leaf), Rhyticeros plicatus (Papua hornbill), Fragaria vesca (wild strawberry)	Gamma radiation	Human white blood cells	Modulating DNA repair pathways	(Szejk-arendt et al., 2020)
9.	Alocasia indica (acacia)	Gamma radiation	Mice	Reduce oxidative stress, cytokinine regulation	(Prasad et al., 2019)
10.	Plumbago zeylanica (Ceylon leadwort)	Gamma radiation	White blood cells	Anti-apoptotic genes	(Checker et al., 2019)
11.	Soybean	Gamma radiation	Rat	Free radical scavenging, reducing inflammation	(Singh & Seed, 2020)
12.	Tea seed	x-ray radiation	Rat	Free radical scavenging	(Martinez et al., 2020)
13.	Garcinia indica	Gamma radiation	Human white blood cells	Free radical scavenging, modulatory	(Baskaware et al., 2024)
14.	Zingiber	Gamma radiation	Rat	Free radical scavenging	(Devi & Sharma, 2022)
15.	Astragalus	x-ray radiation	Bone marrow mesenchymal stem cells	ROS generation, anti-apoptotic	(Zhang et al., 2020)
16.	Moringa oleifera	Gamma radiation	Rat	Reducing inflammation	(Mohammed et al., 2024)
17.	Allium jesdianum (garlic)	Gamma radiation	Pancreas	Reducing inflammation	(Roshankhah et al., 2021)
18.	Aloe vera	Gamma radiation	Mice	Reducing inflammation	(Dadupanthi, 2019)
19.	Panax ginseng	Gamma radiation	Rat	Free radical scavenging, protecting DNA	(Feng et al., 2024)
20.	Avocado peel	Gamma radiation, x-ray radiation	Rat	Free radical scavenging	(Kim et al., 2023)

Table 1 displays the potential and mechanism of plants as radioprotection agent for radiotherapy. There are 20 types of plants that have the potential to be used as radioprotective agents. Out of the 20 plants studied, 14 primarily employed free radical scavenging mechanisms as their main strategy. This highlights the significant role of oxidative stress in radiation damage, where phenolic compounds, such as flavonoids in tea and polyphenols in wine, serve as sacrificial donors to neutralize reactive oxygen species (ROS). The findings highlight a significant drawback: the protective mechanism is generic rather than tailored to specific types of DNA damage. In contrast to synthetic agents like amifostine, which selectively boost glutathione levels in healthy tissues, this natural mechanism may unintentionally shield cancer cells by lowering the same intracellular ROS. A study by Checker et al. (2019) on Plumbago zeylanica demonstrated a paradox: anti-apoptotic genes such as Bcl-2, induced by the extract, may promote the survival of cancer cells.

Plants employ three key pathways to protect themselves from stress. The most significant pathway is the neutralization of oxidative stress, observed in 14 out of 20 studied plants. In this process, phenolic compounds like flavonoids and polyphenols function as electron donors, helping to neutralize ROS. For instance, epigallocatechin-3-gallate (EGCG) found in tea inhibits the Fenton reaction by binding to Fe^{2+} ions, which prevents the formation of harmful hydroxyl radicals (•OH). This mechanism is not selective; for example, compounds like curcumin found in turmeric can activate the Nrf2/ARE (Antioxidant Response Element) pathway, which offers protection to both cancer cells and normal cells. Additionally, high doses of such compounds may diminish the effectiveness of radiotherapy, which relies on ROS to destroy cancer cells. In the DNA protection and repair mechanism, certain compounds exhibit specific actions. Sulfated polysaccharides found in brown algae (Dictyota dichotoma) enhance the expression of DNA repair proteins such as ATM (Ataxia Telangiectasia Mutated) and Rad51. These proteins play a crucial role in detecting DNA double-strand breaks (DSBs) and facilitating homologous recombination. On the other hand, saponins derived from ginseng (Panax ginseng) increase the activity of PARP-1 (Poly-ADP Ribose Polymerase), which is important for DNA base repair. A primary challenge lies in the potential for these mechanisms to repair DNA in cancer cells, especially in tumors with mutations in BRCA1/2 that rely on the PARP pathway. To modulate inflammatory and apoptotic responses, certain extracts are used. For example, garlic (Allium jesdianum) inhibits the NF-κB pathway by suppressing IκBα phosphorylation, which prevents the expression of pro-inflammatory genes such as TNF-α and IL-6. In contrast, Plumbago zeylanica promotes the production of the anti-apoptotic protein Bcl-2 in normal cells while having no effect on cancer cells. Additionally, Astragalus is known to suppress caspase-3 in mesenchymal stem cells. However, excessive inhibition of apoptosis can lead to clinical risks, such as tissue fibrosis resulting from the accumulation of fibroblasts that resist cell death.

The radioprotective capabilities of this plant stem from its phytochemical content, including flavonoids, polyphenols, tannins, saponins, saccharides, resveratrol, and hesperidin. These phytochemicals possess properties that may mitigate damage from radiotherapy. Most studies have utilized in vivo models, such as mice, and human white blood cells to assess the susceptibility of the hematopoietic system to radiation. While the results from these studies are physiologically valid, their main limitations are related to the practical application in clinical settings. One significant challenge is the dual nature of radioprotective effects: administering high doses of antioxidants, like Plumbago zeylanica, can potentially protect cancer cells and diminish the effectiveness of cancer therapies. Additionally, variations in response depending on radiation type (gamma vs. X-ray), dose, and biological model necessitate further standardization. The potential of natural products for radioprotection is promising; however, the predominant use of generic mechanisms, such as free radical scavenging, and the absence of tissue selectivity data pose significant challenges for clinical application.

4. CONCLUSION AND RECOMMENDATION

Plants have demonstrated significant potential as radioprotective agents, helping to shield cells and tissues from radiation damage. Analyzing existing literature reveals that various phytochemical compounds found in plants, such as flavonoids, tannins, saponins, alkaloids, saccharides, resveratrol, and hesperidin, exhibit remarkable abilities to capture free radicals, modulate DNA repair pathways, and reduce oxidative stress resulting from exposure to ionizing radiation. Research utilizing both in vivo and in vitro methods in animal models has shown that several plant extracts can protect blood cells, epithelial cells, the liver, kidneys, and other organs, while also enhancing resistance to damage caused by radiotherapy. Plant-derived radioprotective agents offer a relatively safe alternative to synthetic options. However, further research is needed to integrate these agents into clinical practice effectively. This includes developing stable and effective formulations and evaluating their interactions with cancer therapies.

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