REVIEW ARTICLE

Targeting Oxidative Stress in Cancer Management: The Role of Antioxidant Phytochemicals

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ABSTRACT

Background: Oxidative stress is defined as a state where there is an imbalance between the generation of reactive oxygen species (ROS) and the ability of the body to detoxify it and is implicated in cancer initiation, promotion, and resistance to treatment. Although ROS can contribute to tumorigenesis via DNA damage and oncogenic signaling, they can also cause cancer cell death at high concentrations, making oxidative stress a multifaceted and crucial target in cancer therapy. Phytochemicals that have antioxidant properties, which are naturally present in plants, have the potential to target oxidative stress and enhance cancer treatment. **Aim**: This review focuses on how oxidative stress is involved in cancer development and progression and the paradoxical effects of ROS in tumour cells. It assesses the ability of antioxidant phytochemicals, such as polyphenols, flavonoids, and carotenoids, to reduce oxidative stress, influence important signaling pathways, and improve the effectiveness of conventional cancer treatments. **Method**: Scientific databases such as Web of Science, PubMed, and Scopus, were used, and peer-reviewed literature published within ten years were collected. **Results**: Based on this study, natural antioxidants present in phytochemicals like curcumin, resveratrol, and green tea polyphenols, have been reported to possess therapeutic properties that include reducing oxidative stress, modulating various signaling pathways, and improving cancer treatment outcomes. **Conclusion**: This review explores the potential of antioxidant phytochemicals in cancer treatment, aiming to create more effective therapeutic approaches and address existing hurdles. It guides clinicians and researchers on the appropriate application of these compounds for personalized and holistic cancer treatment.

Keywords: Oxidative stress, Cancer, ROS, Antioxidants, Apoptosis, Phytochemicals.

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INTRODUCTION

Cancer is a general term used to refer to a disease that is marked by the unrestrained proliferation and dispersion of unusual cells in the body. It can involve any organ, and its evolution may be very variable depending on the location and the histological type. Cancer is usually divided into different categories depending on the type of cell or organ it occurs in; these include carcinomas, which are cancers that affect epithelial cells; sarcomas, which are cancers that affect connective tissues; leukaemias, which are cancers that affect blood or bone marrow; and lymphomas, which are cancers that affect lymphatic system [1,2]. Cancer ranks among the most lethal diseases globally. It affects millions of people, and about 10 million of patients die every year due to this disease [3]. In 2020, around 19.3 million new cancer cases and 10 million cancer fatalities were recorded worldwide [4]. Cancer affects both developed and developing countries [5]. Cancer mortality is predominantly concentrated in low- and middle-income regions, where the bulk of cancer-related deaths occur. This disparity frequently results from insufficient access to diagnostic and treatment options [6]. Some of the cancers that are seen more often include lung cancer, breast cancer, colon cancer, prostate cancer, and stomach cancer [7]. Lung cancer continues to be a major issue, with more than two million new cases and 1.7 million fatalities globally in 2018 [8]. Cancer death rates exhibit significant variation among countries, with infection-related and tobacco-related malignancies demonstrating disparities of up to 10-fold [9]. Despite a decline in mortality rates for most significant malignancies in recent years, lung cancer in females and liver cancer in males persistently increase in numerous countries [9]. Tobacco use, poor diet and obesity, lack of physical activity, environment and workplace, genetics and family history, are risk factors of cancer [10]. Common diagnostic methods include imaging, biopsy, blood tests, and hormone therapy [11]. Cancer is costly, and the burden of costs may be categorised into diagnostic costs, therapy costs, and long-term survival costs. Healthcare disparities are caused by factors such as location, affluence, and healthcare access and availability, which lead to increased mortality rates in low- and middle-income countries [12]. To prevent and reduce the increasing global cancer burden, it is necessary to implement measures such as prevention, screening, early detection, and improved care delivery [13].

Notwithstanding advancements in oncological interventions, the global incidence of cancer-related fatalities persists in its upward trajectory, accompanied by alarming projections of further increases. Consequently, there is an imperative necessity to devise innovative tactics that would surpass the efficiency of current methodologies. Considering the pivotal role of oxidative stress in the initiation, progression, and promotion of cancer, it is a better target for cancer therapy. Some phytochemicals have antioxidant properties and are therefore proposed as superior alternatives to conventional cancer therapies or as synergistic agents when used in conjunction with standard medications.

Oxidative stress is a cancer process characterised by an imbalance between the generation of reactive oxygen species [ROS] and their detoxification. This imbalance is recognised to induce gene alterations, promote cancer cell proliferation, and develop resistance to chemotherapy [14]. While ROS are crucial for many biological processes, they are also dangerous and cause damage when their levels are too high, leading to cancer and other diseases. This can cause DNA double-strand breaks, activate oncogenes, and silence tumour suppressor genes [15]. The potential of targeting oxidative stress as an anticancer therapy could also improve the outcome of cancer treatments while minimising their adverse effects. Oxidative stress is one of the critical factors that contribute to cancer progression, and ROS can have both promotional and inhibitory effects on cancer [16]. If the processes of oxidative stress regulation were better understood, it would be possible to create more effective therapeutic approaches and enhance the efficacy of existing treatments as well as reducing adverse effects. Natural antioxidants in phytochemicals like curcumin, resveratrol, and green tea polyphenols, have been reported to possess therapeutic properties that include reducing oxidative stress, modulating various signaling pathways, and improving various disease treatment outcomes [17,18]. Yet, it is important to emphasise that their role in cancer treatment remains confined. An evaluation of the existing research on antioxidant

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phytochemicals embracing oxidative stress might clarify the significance of reactive oxygen species [ROS] in cancer therapy and the potential of antioxidants to enhance the outcome of treatment. Such antioxidant phytochemicals may also enhance the efficacy of conventional therapies such as chemotherapy and radiation by counteracting the adverse effects of ROS in normal cells and making cancer cells more vulnerable to ROS-mediated apoptosis. This review will also aid in addressing existing literature gaps and guide clinicians and researchers on the appropriate application of these compounds in cancer therapy, with the aim of developing more personalised and holistic therapeutic approaches.

1. Methodology/Literature Search Strategy

Database Selection and Keywords: This narrative review aims at evaluating the possibility of using antioxidant phytochemicals in cancer prevention and therapy by regulating oxidative stress. This review synthesised the current scientific evidence on oxidative stress, ROS, and antioxidant phytochemicals in cancer through a thorough search of scientific articles. The scientific databases such as PubMed, Scopus, and Web of Science were searched, and peer-reviewed literature published within eight years were collected. Relevant keywords used were: oxidative stress, antioxidant phytochemicals, cancer management, cancer therapy, phytochemicals, and specific phytochemicals like curcumin, resveratrol, and green tea polyphenols.

Search criteria, inclusion criteria, and exclusion criteria: In order to improve the analysis, it only included articles that were published in scientific journals in the last decade. The review included only studies that were directly related to the role of oxidative stress in cancer, examined the effects of specific antioxidant compounds on cancer cells, provided information on the mechanisms of action, explored the potential application of antioxidant phytochemicals in cancer treatment, or addressed limitations on their use in cancer treatment. Studies pertaining to cancer or oxidative stress, conducted in languages other than English, and studies without adequate details on their study procedures were not selected.

Data Extraction, Synthesis, and Analysis: The data collected was then grouped and arranged in a manner that would enable the reader to easily grasp the various factors that may lead to oxidative stress and the role of antioxidant phytochemicals in cancer treatment. In order to draw conclusions about trends, gaps in the literature, and future research directions, the review provided the implications of the findings. Concluding remarks were made about the function of antioxidant phytochemicals in addressing oxidative stress in cancer, together with suggestions for further investigation and application.

2. The Role of Oxidative Stress in Cancer Initiation and Progression

Oxidative stress is a state of disequilibrium between the formation of reactive oxygen species [ROS] and the ability of the cell to detoxify them. Although ROS are crucial for numerous physiological functions, overproduction of ROS can harm cellular macromolecules such as DNA, proteins, and lipids, causing various diseases, including cancer [15]. Oxidative stress is also involved in the development of cancer through several pathways.

i. DNA Damage and Genomic Instability: A number of mechanisms have been proposed through which oxidative stress contributes to cancer, including DNA damage, base modifications, strand breaks, and cross-linking [19]. Free radicals such as hydroxyl radicals and superoxide anions can cause DNA damage through the breakage of the DNA backbone and can result in the activation of oncogenes or the inactivation of tumour suppressor genes. These genetic changes can cause cancer by promoting cell growth and division [20]. For example, mutations in the TP53 gene that encodes the tumour protein p53 are commonly associated with oxidative stress [21]. ROS may lead to mutagenesis or modulation of the epigenome of tumour suppressor genes, thus leading to their inactivation and cancer initiation. Mutations in cell cycle control genes such as p53 or PTEN result in uncontrolled cell growth and the initiation of cancer [22].

ii. Activation of Oncogenic Pathways: Oxidative stress has been shown to trigger several signalling pathways that are involved in the survival, growth, and spread of cancer cells. Key pathways influenced by ROS include the stimulation of the mitogen-activated protein kinase [MAPK] pathways that will result in cell growth and cell survival [23]. Similarly, the phosphoinositide 3-kinase

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[PI3K]/AKT pathway is involved in cell growth, survival, and metabolism, which is mediated by ROS. ROS can trigger the activation of NF-κB, a protein that controls the expression of genes that are involved in inflammation, cell survival, and cancer progression [24].

iii. Tumor Microenvironment and Angiogenesis: Oxidative stress has an important impact on the formation of the tumour microenvironment. It can also stimulate the production of pro-inflammatory cytokines, growth factors, and matrix metalloproteinases [MMPs], which support tumour growth and new blood vessel formation [25]. According to Ghalehbandi et al. [26], with the stimulation of the production of vascular endothelial growth factor [VEGF], the ROS can help create new blood vessels that the tumour needs to sustain its growth and spread.

iv. Epithelial-to-Mesenchymal Transition [EMT]: With the epithelial-to-mesenchymal transition [EMT], a process that is known to be driven by oxidative stress, cancer cells can acquire migratory and invasive properties [27]. It has been reported that ROS can stimulate the expression of transcription factors, including Snail, Slug, and Twist, that suppress the expression of epithelial markers and promote the expression of mesenchymal markers [28]. EMT is linked to enhanced tumour aggressiveness and apoptosis evasion [29].

3. Rationale for Targeting Oxidative Stress in Cancer Management and Therapy

Oxidative stress is an essential element in cancer development and progression. Oxidative stress has come to be recognised as a promising approach to cancer prevention and therapy aimed at preventing cancer cell proliferation, enhancing the efficacy of other anticancer agents, and decreasing their side effects. The rationale for this strategy is based on an understanding of the key role of oxidative stress in cancer biology. Thus, the redox status can be modulated selectively in the tumour tissue, making the conditions unfavourable for cancer cells only [30]. Generally, tumour cells have a higher amount of ROS and different antioxidant systems than regular cells. This can be employed to enhance the production of ROS in cancer cells only and reduce injury to the healthy tissues of the body [31]. Thus, by enhancing the oxidative stress selectively within the cancer cells, it will be easier to enhance the responsiveness of the cancer cells to other treatments that depend on ROS in eradicating cancer cells [16]. When combined with chemotherapeutic or radiotherapeutic agents, the administration of oxidative stress modulators can enhance the effectiveness of the treatment [32]. For instance, some antioxidants are capable of targeting and eliminating cancer cells without adversely affecting normal cells, thus reducing side effects and perhaps enhancing the effectiveness of treatment. Furthermore, antioxidants are useful in reducing the side effects of normal cells during cancer treatments, improving the quality of life of patients, and allowing them to undergo longer and more rigorous treatments [33]. Creating drugs that target redox signalling pathways in cancer cells may help to stop tumour growth and cell division. For example, inhibition of redox-sensitive proteins like NF-κB leads to reduced inflammation and increased cancer progression [34]. Curcumin, resveratrol, and green tea polyphenolic compounds are some of the antioxidant agents that have therapeutic potential by modulating oxidative stress and cancer-related pathways [35].

4. Therapeutic Challenges in Targeting Oxidative Stress

While targeting oxidative stress presents a potential therapeutic avenue, it also poses significant challenges.

i. Dual Role of ROS: High levels of ROS can enhance cancer progression through oxidative stress, but at the same time, cancer cells can undergo apoptosis by high ROS level. This duality of ROS is harnessed in the treatments of cancer where the intention is to raise ROS levels to a toxic level [36]. For instance, chemotherapy and radiation therapy produce ROS to kill cancer cells and promote apoptosis. But the limitation is that normal cells are also affected by ROS and are prone to damage [32].

ii. Antioxidant Defence Mechanisms: Cancer cells are known to increase their antioxidant defence mechanisms to neutralise ROS so as to survive an oxidative state. Some major antioxidants are superoxide dismutase [SOD], catalase, and glutathione. Thus, these defences can be upregulated to allow cancer cells to evade ROS-mediated apoptosis and make the cancer cells more virulent. This is a problem for therapies that use ROS to

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kill cancer cells [37].

iii. Resistance to Therapy: Certain cancer cells exhibit resistance to oxidative stress, resulting in their failure to undergo apoptosis when exposed to conventional cancer therapy. Cancer cells can elude cell death mediated by ROS by upregulating antioxidant enzymes, activating the NRF2 signalling cascade, and increasing GSH levels. These adaptive responses can be targeted to counteract therapy resistance, which is a significant advantage of the strategy [38].

5. Key Antioxidant Phytochemicals in Cancer management and their Mechanisms of Action

Recent research by Marino et al. [39] emphasises the potential of phytochemicals in the treatment of cancer. Plant substances with inherent antioxidant characteristics have the ability to modulate molecular pathways connected with the initiation and progression of cancer [40]. Through the induction of cell cycle arrest, apoptosis, and autophagy, phytochemicals have demonstrated potential in cancer prevention and management [41]. Furthermore, they have the ability to regulate the balance of reactive oxygen species [ROS], resulting in predetermined cell death in cancer cells [40]. Furthermore, phytochemicals have shown the capacity to counteract harmful epigenetic control, enhance detoxification, regulate inflammation reactions, and alter gut microbiota [42]. Although certain phytochemicals, such as taxol analogues and vinca alkaloids, are currently employed in cancer treatment, current research endeavours to identify and advance novel phytochemical-derived chemotherapy medications [41]. Nonetheless, further investigation is required to comprehensively grasp their modes of action and their synergistic impacts with traditional cancer therapies [39].

Oxidative stress is a process proposed to be influenced by some of the phytochemicals, which are bioactive compounds found in plants. Examples are resveratrol, curcumin, and EGCG, which are polyphenolic antioxidants that are derived from plants [43]. Resveratrol is a phytoalexin present in grapes and berries and has been seen to exhibit anti-cancer capacities, pro-apoptosis effects, and anti-inflammatory effects [44]. Curcumin a family member of compounds called curcuminoids, originating from the root of Curcuma longa, popularly called turmeric. It is associated with anti-inflammatory and antioxidant actions. It has been utilized in the treatment of multiple forms of cancers like breast, colon, and prostate cancer [45]. Epigallocatechin gallate [EGCG], which is one of the most efficacious antioxidants in green tea, has been found to prevent and suppress cancer and cancer metastasis in various types of cancer [46]. Quercetin, genistein, and luteolin are some of the flavonoids that are derived from fruits, vegetables, and herbs. Quercetin has also been described as inhibiting cell proliferation, inducing apoptosis, and having anti-inflammatory properties [47]. Genistein is an isoflavone, a soy product that is believed to assist in the control of hormone-sensitive cancers and has antioxidant effects [48]. Luteolin is another bioactive compound found in celery, broccoli, and peppers and has anti-inflammatory, antioxidant, as well as anti-cancer potentials [49]. Some of the carotenoids such as beta-carotene, lycopene, and astaxanthin, are very useful in cancer care as they have antioxidant properties [50]. The mechanisms of action of these phytochemicals are as follows:

I. ROS Scavenging: Antioxidant phytochemicals primarily act by scavenging ROS, which, if not neutralised, can lead to oxidative stress on the cellular components. This way, they can inhibit the production of ROS, which can lead to DNA changes that promote cancer growth [51].

II. Modulation of Signalling Pathways: Phytochemicals modulate various signal transduction pathways that control cell proliferation, cell survival, and metastasis. For example, curcumin and resveratrol, which are polyphenols, can inhibit NF-κB signalling and therefore reduce inflammation and cancer formation [52]. Some flavonoids like quercetin, can alter tumour suppressor proteins and inhibit oncogenic signalling pathways [53].

III. Induction of Apoptosis: Some antioxidant phytochemicals have been identified to induce cancer cell death through apoptosis. This is done through processes such as enhanced expression of pro-apoptotic proteins, reduced expression of anti-apoptotic proteins, and activation of caspases, enzymes essential in apoptosis [54].

IV. Anti-Angiogenesis and Anti-Metastasis: Luteolin and EGCG have been seen to inhibit angiogenesis [the formation of new blood vessels that supply tumours] and metastasis [the spread of cancer to other parts of the

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body]. These effects are useful in controlling cancer growth and improving the well-being of the affected individuals [55].

6. Potential Benefits of Antioxidant Phytochemicals in Cancer Management

Several researches have established the prospect of antioxidant phytochemicals in cancer prevention and treatment.

i. Prevention: Certain phytochemicals that have antioxidant activity may act as anticancer agents through the regulation of oxidative stress and inflammation, which are characteristics of cancer cells. Thus, some fruits, vegetables and other plant derived food products have been identified to have potential in the prevention of various kinds of cancer and therefore may be useful in cancer control [56].

ii. Adjunctive Therapy: The antioxidant phytochemicals can also be used to increase the potency of the conventional anti-cancer drugs and decrease the adverse effects of these drugs. For instance, curcumin has been observed to enhance the efficacy of radiotherapy and chemotherapy and at the same time, minimize the chances of harming normal cells. This can enhance the therapeutic ratio of standard treatments [57].

iii. Reducing Therapy-Related Toxicity: Some may have antioxidant properties that can assist in reducing the adverse effects of cancer treatments [58]. Some adverse effects of chemotherapy and radiation therapy are fatigue, nausea, and organ dysfunction due to oxidation stress in the normal tissues [59]. Some of the side effects can be managed by using certain antioxidant phytochemicals to enhance the standard of life of cancer patients during the course of therapy.

7. Challenges and Considerations

There are some drawbacks to the use of phytochemicals in cancer treatment, one of which is bioavailability. Many phytochemicals possess low bioavailability, a short half-life, and poor tissue penetration, which may affect their pharmacological efficacy. Other strategies for enhancing its bioavailability, such as nanoemulsion and coadministration with other molecules, are also being explored [60]. Again, antioxidant phytochemicals may work in different ways depending on the concentration, where a low concentration is considered good and a high concentration is considered bad. It is, therefore, crucial to identify the right dosage to ensure effectiveness and safety in cancer prevention and treatment [61]. While antioxidant phytochemicals could enhance the effectiveness of conventional therapies, they could also have the adverse effect of reducing the effectiveness of these treatments. For example, cancer cells can resist apoptosis through exposure to ROS during chemotherapeutic treatment due to high antioxidant levels [62]. It is vital that the timing, the amount, and the other drugs to be administered in combination with the drug of concern be well considered to avoid any unfavourable effects. It has been known that tumour cells can develop resistance to oxidative stress-based therapies, and thus, there is a need for more research [63].

Conclusion

Oxidative stress has come to light as a viable target for enhancing cancer treatment, but it is also a challenging goal. Antioxidant phytochemicals present a potentially safe and useful approach to preventing oxidation, improving cancer treatment, and decreasing side effects from therapy. Over time, these compounds might form the basis of a complete cancer treatment strategy and enhance the standard of life for cancer patients.

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