The Interplay of Vitamins, Antioxidants, and Nutrient Metabolism in Tumorigenesis and Cancer Therapy: A Survey

Abstract

This survey paper explores the intricate relationship between vitamins, antioxidants, nutrient metabolism, and the tumor microenvironment, highlighting their collective influence on cancer development, progression, and therapy. Vitamins, as essential micronutrients, play a crucial role in cellular homeostasis and immune modulation, impacting tumorigenesis through deficiencies or excesses that alter immune function. Antioxidants, while known for neutralizing oxidative stress and preventing DNA damage, have a dual role as they can also exhibit pro-oxidant effects under certain conditions, potentially contributing to cancer progression. The paper delves into the metabolic reprogramming characteristic of cancer cells, such as the Warburg effect, and the role of lipid and amino acid metabolism in supporting tumor growth and survival. It further explores the tumor microenvironment's influence on nutrient metabolism and cancer resilience, emphasizing the competition for resources between cancer and immune cells. Additionally, the survey examines the potential of integrating antioxidants and phytochemicals into targeted therapy regimens, highlighting their role in modulating oxidative stress and signaling pathways to enhance treatment efficacy and reduce side effects. The paper concludes by discussing the therapeutic implications of these complex interactions, emphasizing the need for further research to develop targeted interventions that exploit the metabolic vulnerabilities of cancer cells. This comprehensive understanding of the interplay between vitamins, antioxidants, nutrient metabolism, and the tumor microenvironment is crucial for advancing cancer prevention and therapy, ultimately improving patient outcomes and addressing global disparities in cancer care.

1 Introduction

1.1 Significance of Vitamins and Antioxidants in Cancer Biology

Vitamins and antioxidants are fundamental in cancer biology, influencing tumorigenesis and therapeutic outcomes. As essential micronutrients, vitamins are vital for cellular homeostasis and immune modulation, with imbalances potentially promoting tumorigenesis [1]. The preservation of vitamins such as C, E, K, and beta-carotene during food preparation is crucial for their protective effects against oxidative stress [2].

Antioxidants play a key role in mitigating oxidative stress, a significant factor in cancer development. By neutralizing free radicals, they prevent DNA damage and cancer initiation; however, their dual role as potential pro-oxidants under certain conditions complicates their relationship with cancer progression [3]. This complexity is particularly evident in aggressive cancers like glioblastoma multiforme, where understanding antioxidant interactions is vital for improving treatment outcomes [4].

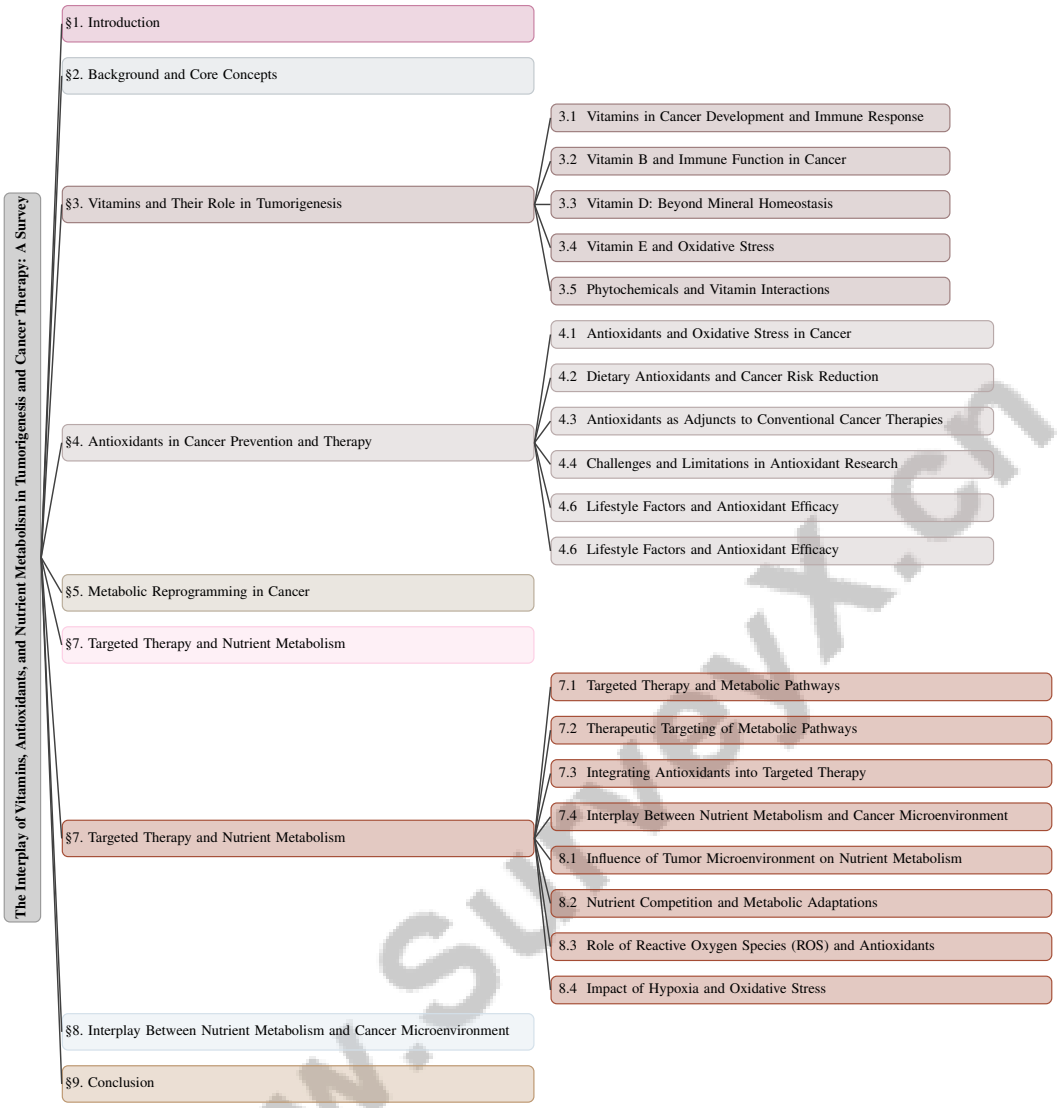

Figure 1: chapter structure

The relationship between dietary factors, including vitamins and antioxidants, and cancer prevention, treatment, and recurrence is a critical area of research, especially in breast cancer studies [1]. Antioxidants are increasingly recognized for their potential across various fields, including food technology and health, emphasizing their role in combating oxidative stress and promoting health benefits.

Reactive oxygen species (ROS), metabolic byproducts, are central to discussions on antioxidants in cancer biology. ROS can both promote and suppress tumorigenesis, underscoring their complex role in cancer initiation and progression [3]. Understanding the regulatory networks involving oxidative stress and ROS is essential for developing effective cancer therapies [5].

Beyond their direct effects on cancer cells, vitamins and antioxidants influence the tumor microenvironment and systemic factors that contribute to cancer resilience and fragility [6]. This survey aims to elucidate these complex interactions and address existing knowledge gaps in cancer treatment mechanisms. Furthermore, exploring the roles of these nutrients in cancer biology enhances our understanding of tumorigenesis and informs the development of targeted therapies and preventive strategies, particularly addressing global disparities in cancer prevention in low-income countries [7].

AI-generated, for reference only.

1.2 Structure of the Survey

The survey is structured into key sections, each addressing critical aspects of the interplay between vitamins, antioxidants, and nutrient metabolism in cancer biology. The introduction highlights the significance of these elements in tumorigenesis and cancer therapy. Following this, the survey provides a comprehensive overview of nutrient metabolism relevant to cancer biology, defining essential terms such as tumorigenesis, metabolic reprogramming, and targeted therapy.

Subsequent sections focus on the roles of specific vitamins in cancer development, particularly their effects on immune response and oxidative stress, examining vitamins B, D, and E, along with the interactions between phytochemicals and vitamins. The discussion then shifts to antioxidants, exploring their dual role in cancer prevention and therapy, while addressing challenges and limitations in antioxidant research.

The narrative progresses to metabolic reprogramming in cancer, analyzing how cancer cells alter their metabolism to support growth and survival. The following section delves into targeted therapy and nutrient metabolism, emphasizing strategies that exploit the metabolic flexibility of cancer cells to enhance treatment efficacy. This exploration highlights how cancer cells adapt their nutrient acquisition and processing mechanisms in response to environmental changes, which can be strategically targeted to improve patient outcomes in precision oncology [8, 9, 10].

The survey further investigates the interaction between nutrient metabolism and the tumor microenvironment, examining factors such as ROS, hypoxia, and oxidative stress. The conclusion synthesizes findings, discussing implications for cancer therapy and prevention while suggesting future research directions. Through this structured approach, the survey seeks to elucidate the intricate relationships among vitamins, particularly B vitamins, antioxidants, and nutrient metabolism, and their roles in cancer biology, highlighting influences on cellular processes, immune regulation, and tumorigenesis, as well as the potential pro- and antitumorigenic effects associated with ROS and antioxidant activity [11, 12, 1, 13].The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Nutrient Metabolism and Cancer Biology

Nutrient metabolism is integral to cancer biology, influencing both tumorigenesis and therapeutic efficacy. Cancer cells undergo metabolic reprogramming, marked by increased glycolysis, glutaminolysis, and lipid biosynthesis, to meet their elevated energy and biosynthetic requirements for rapid proliferation. This metabolic adaptability allows cancer cells to adjust to fluctuating nutrient levels, utilizing the same nutrient through multiple pathways [10].

Amino acids are pivotal in cancer metabolism, acting as substrates for protein synthesis and modulators of signaling pathways. Restricting specific dietary amino acids has emerged as a potential strategy to inhibit cancer growth and improve therapeutic outcomes, underscoring the complex relationship between nutrient availability and cancer metabolism [14]. Cancer cells also exhibit altered glucose metabolism, characterized by increased glucose uptake and lactate production, even under aerobic conditions—a phenomenon known as the Warburg effect. This shift is regulated by pathways such as ERK and JNK, which are implicated in cancer progression and inflammation [15].

Lipid metabolism plays a significant role in cancer biology, where lipid accumulation can induce metabolic paralysis in immune cells, such as natural killer (NK) cells, impairing their antitumor functions [16]. Lactate, a byproduct of anaerobic glycolysis, further influences immune cell function and the tumor microenvironment, impacting immune surveillance and cancer progression [17].

The tumor microenvironment significantly affects cancer metabolism, with mitochondrial dysfunction and mitophagy being critical in tumor development and metastasis [18]. Metabolic pathways in cancers, such as prostate cancer, are shaped by genetic alterations, environmental factors, and the tumor microenvironment [19]. Oxidative stress, driven by reactive oxygen species (ROS), is a key factor in cancer processes, including tumorigenesis and metastasis [20].

Phytochemicals from dietary sources, particularly cruciferous vegetables, have been studied for their ability to modulate cancer cell metabolism and possess chemopreventive properties. These compounds offer promising avenues for cancer prevention and therapy by disrupting cancer metabolism.

Additionally, the gut microbiota's metabolism of dietary components highlights the complex interactions between diet and cancer metabolism [21].

The Western diet, characterized by high processed food intake and low fruit and vegetable consumption, correlates with increased cancer risk, emphasizing the importance of nutrient metabolism in cancer prevention [22]. The interplay between nutrient metabolism and cancer biology not only reveals potential therapeutic targets but also suggests innovative strategies to disrupt cancer cell metabolic dependencies, paving the way for novel cancer treatment and prevention approaches.

2.2 Tumorigenesis, Metabolic Reprogramming, and Targeted Therapy

Tumorigenesis is a complex process driven by genetic mutations, epigenetic changes, and environmental factors that transform normal cells into malignant ones [23]. This transformation is further complicated by tissue heterogeneity, affecting interactions between cancer cells and their microenvironment. Cancer stem cells (CSCs) contribute to this heterogeneity, often leading to increased malignancy and resistance to conventional therapies [24].

Metabolic reprogramming is a hallmark of cancer, enabling cells to modify their metabolic pathways to meet increased energy and biosynthetic demands essential for rapid proliferation. This reprogramming includes enhanced glycolysis, glutaminolysis, and lipid biosynthesis, crucial for tumor growth and metastasis. The Warburg effect, characterized by a shift to aerobic glycolysis, is regulated by signaling pathways such as ERK and JNK, which are also involved in chemotherapy and radiotherapy resistance [15]. The role of SIRT6 in regulating apoptosis and nutrient deprivation further illustrates the connections between metabolic pathways and cancer cell survival [25].

Targeted therapy represents a promising approach in cancer treatment, focusing on specific molecular and metabolic pathways altered in cancer cells. By targeting these pathways, therapies aim to disrupt cancer cell growth while minimizing damage to normal cells. The dual role of oxidative stress in cancer, both promoting tumorigenesis and serving as a therapeutic target, underscores the potential of targeted interventions [5]. Additionally, the involvement of ROS and inflammasomes in cancer highlights opportunities for targeted therapies to modulate these pathways for therapeutic gain [3].

Phytochemicals from dietary sources offer potential in cancer prevention and treatment by interacting with various molecular pathways involved in carcinogenesis [26]. Incorporating natural compounds into targeted therapy regimens may enhance therapeutic efficacy and provide a holistic approach to cancer treatment, addressing both metabolic and molecular abnormalities in cancer cells. Furthermore, the metabolic competition between cancer cells and immune cells significantly influences the immune response against tumors, adding complexity to the development of effective cancer therapies [27]. Investigating the modularity of the metabolic gene network has potential implications for prognostication in hepatocellular carcinoma, aiming to identify predictive biomarkers for cancer recurrence and patient survival [28]. Understanding these intricate interactions is essential for advancing targeted therapy strategies and improving patient outcomes.

The intricate relationship between vitamins and tumorigenesis has garnered significant attention in recent research. As depicted in Figure 2, this figure illustrates the hierarchical structure of vitamins and their roles in tumorigenesis, highlighting key categories such as immune response modulation, oxidative stress management, and interactions with phytochemicals. The illustration emphasizes the multifaceted impact of vitamins B, D, and E in cancer prevention and therapy, alongside the potential synergistic effects of phytochemicals and the gut microbiota in enhancing antioxidant defenses and modulating immune function. By examining these interactions, we can better understand the complex mechanisms through which vitamins contribute to cancer biology and inform future therapeutic strategies.

3 Vitamins and Their Role in Tumorigenesis

3.1 Vitamins in Cancer Development and Immune Response

Vitamins play a pivotal role in modulating immune responses and influencing cancer development. Deficiencies or excesses in vitamins can significantly impact tumorigenesis. Vitamin B deficiencies, for example, impair immune responses and exacerbate disease severity, as demonstrated in COVID-19 cases [29]. Adequate B vitamin levels are crucial for optimal immune function and potentially

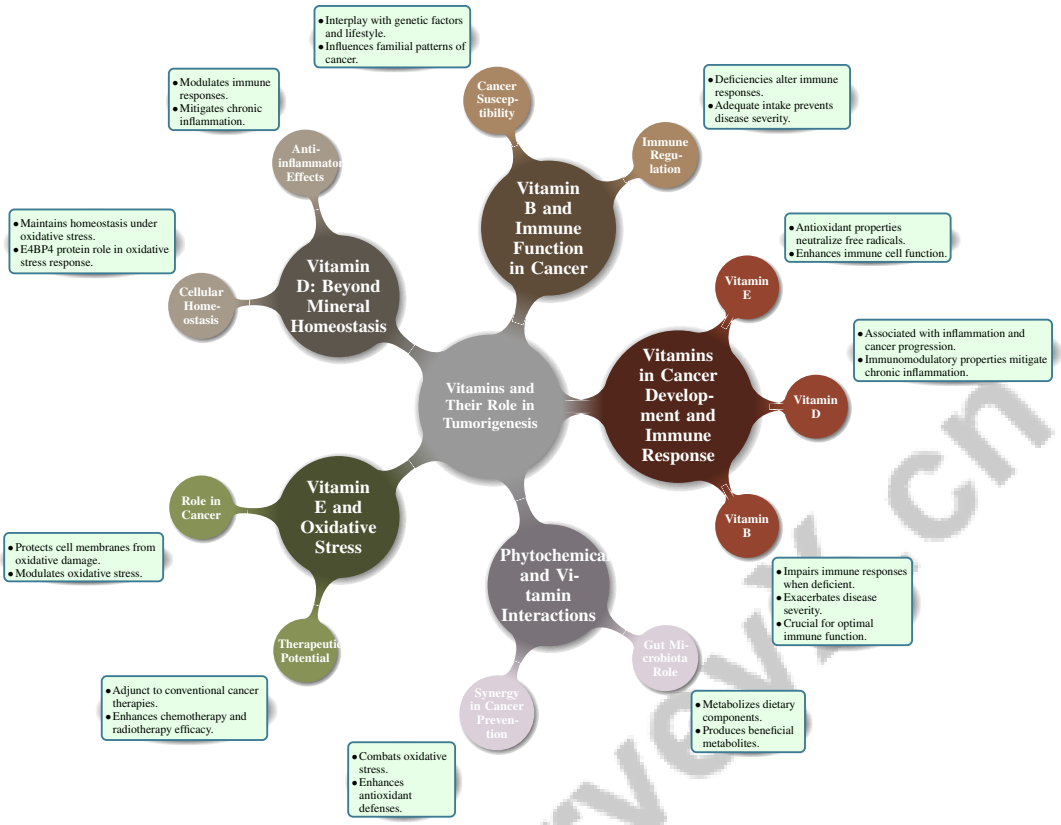

Figure 2: This figure illustrates the hierarchical structure of vitamins and their roles in tumorigenesis, highlighting key categories such as immune response modulation, oxidative stress management, and interactions with phytochemicals. It emphasizes the multifaceted impact of vitamins B, D, and E in cancer prevention and therapy, alongside the potential synergistic effects of phytochemicals and the gut microbiota in enhancing antioxidant defenses and modulating immune function.

reducing cancer risk [12]. Similarly, vitamin D deficiency is associated with inflammation and cancer progression, complicating clinical practices due to the lack of consensus on treatment serum levels [30]. Vitamin D's immunomodulatory properties mitigate chronic inflammation, a known promoter of various cancers [31].

Vitamin E, known for its antioxidant properties, neutralizes free radicals and reduces oxidative stress, a factor in cancer development. Studies suggest that vitamin E enhances immune cell function and modulates immune responses, which are crucial for preventing immune evasion by cancer cells [32]. Moreover, cooking methods like blanching, boiling, and steaming affect vitamin retention in vegetables, influencing their effectiveness in cancer prevention [2].

To further elucidate these concepts, Figure 3 illustrates the roles of vitamins B, D, and E in cancer development and immune response, highlighting their specific impacts such as immune modulation, inflammation control, and antioxidant properties. The figure also notes the influence of cooking methods on vitamin retention, underscoring the importance of both dietary sources and preparation techniques in optimizing vitamin efficacy in cancer prevention [33].

3.2 Vitamin B and Immune Function in Cancer

Vitamin B is essential for immune function and significantly impacts cancer development. Its roles in immune regulation are well-documented, with deficiencies or excesses altering immune responses and potentially contributing to cancer progression [12]. Adequate vitamin B intake is crucial for a healthy immune system, potentially preventing or mitigating disease severity [29]. Sufficient B vitamin levels are vital for the functioning of immune cells like T and B cells, influencing immune

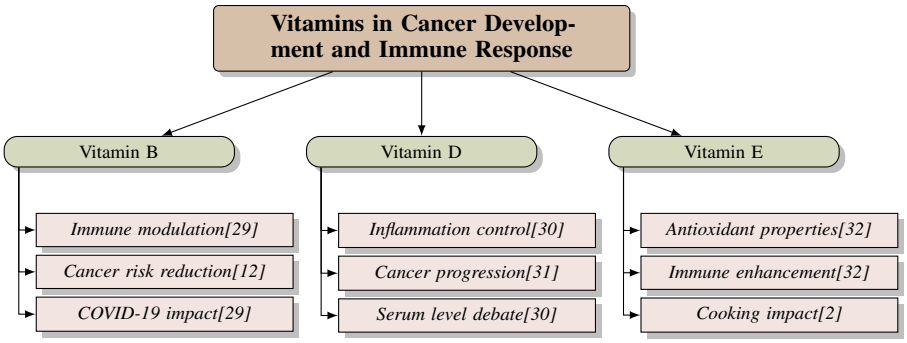

Figure 3: This figure illustrates the roles of vitamins B, D, and E in cancer development and immune response, highlighting their specific impacts such as immune modulation, inflammation control, and antioxidant properties. The figure also notes the influence of cooking methods on vitamin retention.

cell regulation and elucidating the complex relationship between nutrition and cancer development [34, 12].

The interplay between vitamin B levels and genetic factors, alongside lifestyle and dietary habits, can affect individual cancer susceptibility. Familial patterns of cancer, such as gastric cancer, may also be influenced by nutritional status, including vitamin B levels [35]. This suggests that personalized nutritional strategies could enhance immune function and reduce cancer risk.

3.3 Vitamin D: Beyond Mineral Homeostasis

Vitamin D significantly influences cancer biology beyond its traditional role in mineral homeostasis [36]. Recent studies highlight its roles in modulating immune responses and exerting anti-inflammatory effects crucial for cancer prevention and therapy. The vitamin D metabolome, comprising various metabolites in human serum, is vital for understanding its complex biological activities, mediated by cytochrome P450 enzymes [37].

Vitamin D's anti-inflammatory properties are particularly relevant, as chronic inflammation is a recognized driver of tumorigenesis [34]. By modulating inflammatory responses, vitamin D may help mitigate chronic inflammation that contributes to cancer initiation and progression [36]. Additionally, vitamin D is critical for maintaining cellular homeostasis under oxidative stress and DNA damage conditions [36]. The E4BP4 protein, regulated by the E4BP4 gene, plays a role in cellular responses to oxidative stress and DNA damage, key factors in cancer development.

The diverse roles of vitamin D across various populations, including vulnerable groups like infants and pregnant women, emphasize the need for further research to understand its potential in cancer prevention and therapy [30]. Developing a comprehensive framework to categorize vitamin D metabolites based on their enzymatic pathways is essential for advancing our understanding of vitamin D metabolism and its implications in cancer biology [37].

3.4 Vitamin E and Oxidative Stress

Vitamin E, a fat-soluble antioxidant, is crucial for protecting cell membranes from oxidative damage by neutralizing reactive oxygen species (ROS). This role is significant in cancer, where oxidative stress—an imbalance between ROS production and antioxidant defenses—has been identified as a key factor in tumorigenesis. By modulating oxidative stress, vitamin E may regulate cellular processes involved in cancer development and treatment [13, 5, 11, 32, 20].

Oxidative stress influences multiple stages of tumorigenesis, affecting processes such as cell senescence, apoptosis, and the tumor microenvironment. ROS can induce genetic mutations, promote DNA damage, and activate signaling pathways leading to tumorigenesis. Vitamin E, by scavenging free radicals, mitigates oxidative stress and its deleterious effects [5, 11, 38, 3]. Research indicates that vitamin E may reduce oxidative stress and inflammation, both implicated in tumorigenesis [5, 11]. However, the relationship between vitamin E and cancer is complex, exhibiting both protective and pro-oxidant effects depending on context and dosage [5, 11, 1, 13].

Vitamin E's potential as an adjunct to conventional cancer therapies, enhancing chemotherapy and radiotherapy efficacy and reducing associated side effects, underscores the need for further research to effectively harness its therapeutic benefits [20, 5, 11, 38].

3.5 Phytochemicals and Vitamin Interactions

Interactions between phytochemicals and vitamins present a promising avenue for cancer prevention and therapy. Phytochemicals, naturally occurring compounds in plants, have been extensively studied for their antioxidant properties and ability to modulate pathways involved in cancer development and progression [39]. These compounds, including polyphenols and flavonoids, demonstrate significant potential in targeting cancer stem cells and altering the tumor microenvironment.

The synergy between phytochemicals and vitamins is crucial in combating oxidative stress, a key factor in tumorigenesis. Dietary antioxidants from phytochemicals, such as those in cruciferous vegetables, interact with vitamins to enhance antioxidant defenses [33], mitigating oxidative damage from environmental toxins and reducing cancer risk [1]. Despite the promising potential of phytochemicals and vitamins, significant knowledge gaps remain regarding optimal structural characteristics for antioxidant activity and interactions [40]. Understanding these interactions is essential for developing effective dietary strategies.

Moreover, the role of gut microbiota in metabolizing dietary components, including phytochemicals and vitamins, has gained attention. The gut microbiota influences host health by producing beneficial metabolites like short-chain fatty acids, which can modulate immune function and potentially impact cancer development [21]. This underscores the importance of considering the complex interplay between diet, gut microbiota, and cancer biology in developing effective preventive and therapeutic strategies.

4 Antioxidants in Cancer Prevention and Therapy

As the understanding of cancer biology continues to evolve, the focus on antioxidants has garnered significant attention due to their potential role in cancer prevention and therapy. This section delves into the multifaceted interactions between antioxidants and oxidative stress, a critical factor in tumorigenesis. Specifically, we will explore how antioxidants mitigate oxidative stress and their implications for cancer biology, setting the stage for a deeper examination of their role in cancer prevention and treatment strategies in the subsequent subsection.

4.1 Antioxidants and Oxidative Stress in Cancer

Antioxidants play a multifaceted role in cancer biology, primarily through their capacity to mitigate oxidative stress, a significant contributor to tumorigenesis. Oxidative stress arises when the production of reactive oxygen species (ROS) surpasses the body's antioxidant defenses, leading to an imbalance that can cause significant cellular damage [41]. The excess of ROS is known to induce DNA mutations, protein oxidation, and lipid peroxidation, all of which are critical factors in the initiation and progression of cancer .

The protective role of antioxidants against oxidative damage is well-documented, as these compounds neutralize free radicals, thereby preventing the cellular damage that contributes to tumorigenesis. Polyphenols, a class of naturally occurring antioxidants found in many fruits and vegetables, have demonstrated potential in reducing cancer risk due to their ability to scavenge free radicals and modulate signaling pathways involved in carcinogenesis [39]. However, the effectiveness of antioxidants in cancer prevention and therapy is highly context-dependent, influenced by factors such as bioavailability and the specific biological environment in which they are applied [11].

While antioxidants are widely recognized for their health benefits, emerging research indicates that they can also exhibit pro-oxidant effects under specific conditions, potentially facilitating cancer progression instead of prevention. This duality arises from the complex interplay between antioxidants and reactive oxygen species (ROS), where excessive antioxidant supplementation—particularly in individuals without identified oxidative stress—may disrupt cellular signaling and promote tumorigenesis. Studies suggest that antioxidants should be used judiciously, particularly in populations at risk for oxidative stress, as their effects can vary significantly based on context and dosage. [13, 5, 42, 11, 43].

This dual role is particularly relevant in the context of tumor biology, where factors such as the presence of tumor-elicited oxidative neutrophils can maintain their suppressive function even in glucose-restricted environments, thereby influencing cancer progression and resistance to therapy .

The interplay between oxidative stress and antioxidants in cancer is further complicated by the role of reactive oxygen species (ROS) in both promoting and suppressing tumorigenesis . While ROS can drive cancer progression by inducing genetic mutations and activating pro-tumorigenic signaling pathways, they can also be targeted therapeutically to enhance the effectiveness of cancer treatments [5]. The development of more effective antioxidants that can address the imbalance of ROS and antioxidant defenses in cancer cells remains an ongoing challenge for researchers [40].

4.2 Dietary Antioxidants and Cancer Risk Reduction

Dietary antioxidants are recognized for their potential role in reducing cancer risk by counteracting oxidative stress, a well-established factor in cancer pathogenesis. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates, leading to cellular damage and promoting carcinogenesis . Antioxidants, which can be derived from both natural sources such as fruits, vegetables, and herbs, as well as synthetic origins, play a crucial role in cellular health by neutralizing reactive oxygen species (ROS). This neutralization helps to prevent oxidative damage to DNA and other cellular components, thereby inhibiting the activation of signaling pathways that may lead to cancer development. The balance between ROS and antioxidants is vital for maintaining tissue homeostasis, and disruptions in this balance can contribute to tumorigenesis and metastasis. Recent studies have highlighted the importance of understanding the multifaceted roles of both antioxidants and ROS in cancer biology, as well as the potential therapeutic applications of various antioxidant compounds in cancer prevention and treatment. [11, 43, 26, 20, 44]

Polyphenols, a diverse group of naturally occurring compounds found in fruits, vegetables, and other plant-based foods, have been extensively studied for their antioxidant properties. Diets rich in polyphenols have been associated with a reduced risk of cancer, suggesting their potential as chemopreventive agents [39]. These compounds exert their effects through various mechanisms, including the modulation of signal transduction pathways, inhibition of cell proliferation, and induction of apoptosis in cancer cells [39]. However, despite promising findings, further research is necessary to elucidate the specific mechanisms through which polyphenols exert their anticancer effects and to improve their bioavailability for therapeutic applications [39].

The effectiveness of dietary antioxidants in cancer prevention is also influenced by their interaction with other dietary components and lifestyle factors. The gut microbiota plays a crucial role in the metabolism of dietary components, including antioxidants, thereby affecting their bioavailability and biological activity [21]. Understanding the complex interactions between dietary antioxidants, the gut microbiota, and cancer biology is essential for developing effective dietary strategies for cancer prevention [21].

Despite the potential benefits of dietary antioxidants, it is important to recognize the challenges and limitations in this area of research. The bioavailability of antioxidants can vary significantly depending on their chemical structure, the food matrix in which they are consumed, and individual differences in metabolism [39]. Moreover, the impact of metal complexation on antioxidant effectiveness is an area that warrants further investigation, as it may influence the stability and activity of these compounds [40].

In addition to their direct antioxidant effects, dietary components, including vitamins and phytochemicals, can interact with each other and with the gut microbiota, influencing nutrient metabolism and potentially impacting cancer risk [21]. These interactions highlight the importance of a holistic approach to cancer prevention, which considers the complex interplay between diet, nutrient metabolism, and the tumor microenvironment.

4.3 Antioxidants as Adjuncts to Conventional Cancer Therapies

The integration of antioxidants into conventional cancer therapies presents a promising strategy for enhancing treatment efficacy and mitigating adverse effects. Antioxidants, by virtue of their ability to neutralize free radicals, can play a critical role in reducing oxidative stress, which is often exacerbated

by cancer treatments such as chemotherapy and radiotherapy [45]. The computational modeling of cell death due to free radical excess underscores the importance of antioxidants in protecting normal cells during cancer treatment, thereby potentially improving patient outcomes [45].

Recent research has demonstrated that certain polyphenols, a class of naturally occurring antioxidants, not only exhibit anticancer properties but also have the potential to enhance the effectiveness of conventional cancer treatments [39]. These compounds, through their ability to modulate oxidative stress and influence key signaling pathways, can act synergistically with traditional therapies, offering a multifaceted approach to cancer treatment.

Moreover, the structural characteristics of antioxidants, such as the presence of hydroxyl groups and their metal complexation capabilities, play a crucial role in their efficacy [40]. These structural elements enhance the antioxidant properties, suggesting that optimizing these features could further improve their adjunctive potential in cancer therapy.

The combination of antioxidants with other therapeutic agents, such as antithrombotics, has been shown to enhance treatment effectiveness. This approach suggests a novel pathway for adjunctive cancer therapies, where antioxidants help to mitigate treatment-related oxidative stress while potentially enhancing the therapeutic index of standard treatments [4].

In addition to antioxidants, dietary interventions, such as amino acid restrictions, have been explored for their potential to inhibit cancer cell proliferation and enhance the efficacy of existing treatments [14]. These findings highlight the potential of integrating nutritional strategies with conventional cancer therapies to improve outcomes.

Furthermore, the role of vitamin D in supporting bone health and immune function, along with its protective roles against various diseases, underscores its potential as an adjunct in cancer therapy [36]. By modulating immune responses and reducing inflammation, vitamin D may enhance the therapeutic effects of conventional treatments.

4.4 Challenges and Limitations in Antioxidant Research

Antioxidant research in the context of cancer prevention and therapy is fraught with several challenges and limitations, primarily due to the complex nature of oxidative stress and the multifarious roles that antioxidants play in cancer biology. Oxidative stress, a condition resulting from an imbalance between the production of reactive oxygen species (ROS) and the body's capability to neutralize these reactive molecules, is a critical factor in cancer pathogenesis [41]. This imbalance can lead to significant cellular damage, including DNA mutations and the activation of pro-tumorigenic signaling pathways, which are central to cancer initiation and progression .

The dual role of antioxidants as both protective agents and potential pro-oxidants adds a layer of complexity to their study. While antioxidants are widely recognized for their capacity to neutralize free radicals and reduce oxidative damage, recent research indicates that under specific conditions, they can also exhibit pro-oxidant effects, potentially facilitating cancer progression instead of prevention. This paradox arises from the complex roles that reactive oxygen species (ROS) play in cellular processes, where they can contribute to both disease promotion and prevention. Moreover, the efficacy of commonly used antioxidants, such as vitamins C and E, in lowering pathological ROS levels remains uncertain. Consequently, the indiscriminate use of antioxidant supplements, often driven by public distrust in conventional medicine, may not only be unnecessary but could also be harmful, particularly in populations without identified oxidative stress. Therefore, a nuanced understanding of the conditions under which antioxidants function is essential for their appropriate application in cancer prevention and treatment. [5, 20, 42, 13]. This paradox necessitates a nuanced understanding of the specific conditions under which antioxidants can be beneficial or harmful, highlighting the need for further research to elucidate the precise mechanisms underlying their activity in cancer biology .

Despite the potential benefits of antioxidants in cancer prevention and therapy, existing research methods have shown inconsistent correlations between oxidative stress markers and antioxidant capacity, posing a significant challenge to the field [41]. This inconsistency underscores the need for standardized methodologies and more robust experimental designs to accurately assess the role of antioxidants in cancer biology and therapy.

The intricate interactions between antioxidants and various biological pathways, including the E4 promoter-binding protein 4 (E4BP4), mitochondrial functions, and DNA damage response mechanisms, significantly complicate the study of antioxidants in cancer research. This complexity arises from the dual roles of reactive oxygen species (ROS) in tumorigenesis and cellular signaling, where antioxidants can both mitigate oxidative stress and inadvertently promote pro-tumorigenic processes. As recent studies indicate, the aberrant activation of antioxidant programs, such as those regulated by the transcription factor NFE2-related factor 2 (NRF2), further underscores the need for a nuanced understanding of how these interactions influence cancer progression and treatment outcomes. [5, 11, 42, 13]. Understanding these interactions is crucial for developing effective therapeutic strategies that harness the potential of antioxidants in cancer prevention and treatment.

In addition to these scientific challenges, there are also regulatory hurdles that must be addressed to facilitate the development and integration of antioxidants into conventional cancer therapies. The prevailing belief that natural antioxidants are less effective than their synthetic counterparts can significantly impede their development and integration into clinical practice, despite growing evidence highlighting the diverse benefits of natural antioxidants—such as anti-inflammatory and anti-aging properties—alongside their potential for use in food preservation, pharmaceuticals, and cosmetics. Recent studies have demonstrated that natural antioxidants, derived from various plant sources, not only exhibit substantial biological activity but also offer economic advantages by utilizing food by-products and under-exploited plant species. This underscores the need for a shift in perception to fully leverage the potential of natural antioxidants in health and industry applications. [46, 43, 44]. Overcoming these challenges requires a concerted effort to advance research methodologies, improve our understanding of antioxidant mechanisms, and develop evidence-based guidelines for their use in cancer prevention and therapy.

4.5 Lifestyle Factors and Antioxidant Efficacy

Lifestyle factors play a crucial role in modulating the efficacy of antioxidants in cancer prevention and therapy. Diet, physical activity, smoking, and alcohol consumption are key lifestyle factors that can influence the body's oxidative stress levels and, consequently, the effectiveness of antioxidants in mitigating cancer risk [39]. A balanced diet rich in fruits and vegetables, which are natural sources of antioxidants, has been associated with a reduced risk of cancer, highlighting the importance of dietary choices in cancer prevention [22].

Physical activity is another critical lifestyle factor that can enhance the body's antioxidant defenses. Regular exercise has been shown to increase the production of endogenous antioxidants, thereby reducing oxidative stress and potentially lowering cancer risk [33]. Additionally, exercise can modulate immune function, which is essential for the body's ability to detect and eliminate cancer cells [29].

Lifestyle factors such as smoking and excessive alcohol consumption significantly increase oxidative stress, which is characterized by an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses. This heightened oxidative stress has been implicated in the promotion of cancer development through various mechanisms, including the induction of cellular damage and disruption of critical signaling pathways involved in cell fate determination. Consequently, these lifestyle choices not only exacerbate oxidative stress but also enhance the risk of developing various cancers, including lung cancer and gastric cancer, by influencing tumorigenesis and progression through complex biological interactions. [13, 5, 35, 38, 47]. Smoking is a well-established risk factor for various cancers, contributing to oxidative damage and inflammation . Similarly, excessive alcohol consumption is associated with increased oxidative stress and a higher risk of certain cancers, including liver and breast cancer .

The interaction between lifestyle factors and dietary antioxidants is complex, as these factors can influence the bioavailability, metabolism, and efficacy of antioxidants in the body. For instance, the consumption of a diet rich in fruits and vegetables, which are high in antioxidants and phytochemicals, can enhance the body's antioxidant defenses and reduce cancer risk [22]. Conversely, unhealthy lifestyle choices, such as smoking and excessive alcohol consumption, may negate the beneficial effects of dietary antioxidants and exacerbate oxidative stress [46].

Furthermore, the gut microbiota plays a pivotal role in modulating the bioavailability and efficacy of dietary antioxidants. The gut microbiota's ability to metabolize dietary components, including

phytochemicals and vitamins, can significantly influence their biological activity and impact on cancer prevention and therapy [21]. This highlights the importance of considering lifestyle factors, including diet and gut health, in developing effective antioxidant-based interventions for cancer prevention and therapy.

4.6 Lifestyle Factors and Antioxidant Efficacy

Lifestyle factors significantly influence the efficacy of antioxidants in cancer prevention and therapy, highlighting the importance of a holistic approach to health. Diet, physical activity, smoking, and alcohol consumption are key factors that can modulate oxidative stress levels and, consequently, the effectiveness of antioxidants in mitigating cancer risk [46]. A diet rich in fruits, vegetables, and other sources of natural antioxidants has been associated with a reduced risk of cancer, emphasizing the role of dietary choices in cancer prevention [48].

Physical activity is another critical lifestyle factor that can enhance the body's antioxidant defenses. Regular exercise has been shown to increase the production of endogenous antioxidants, thereby reducing oxidative stress and potentially lowering cancer risk [49]. Additionally, exercise can modulate immune function, which is essential for the body's ability to detect and eliminate cancer cells [50].

Conversely, lifestyle factors such as smoking and excessive alcohol consumption can exacerbate oxidative stress and promote cancer development. Smoking is a well-established risk factor for various cancers, contributing to oxidative damage and inflammation. Similarly, excessive alcohol consumption is associated with increased oxidative stress and a higher risk of certain cancers, including liver and breast cancer [13].

The interaction between lifestyle factors and dietary antioxidants is complex, as these factors can influence the bioavailability, metabolism, and efficacy of antioxidants in the body. For instance, the consumption of a diet rich in antioxidants and phytochemicals can enhance the body's antioxidant defenses and reduce cancer risk [46]. Conversely, unhealthy lifestyle choices, such as smoking and excessive alcohol consumption, may negate the beneficial effects of dietary antioxidants and exacerbate oxidative stress [44].

Moreover, the gut microbiota plays a pivotal role in modulating the bioavailability and efficacy of dietary antioxidants. The gut microbiota's ability to metabolize dietary components, including phytochemicals and vitamins, can significantly influence their biological activity and impact on cancer prevention and therapy [51]. This highlights the importance of considering lifestyle factors, including diet and gut health, in developing effective antioxidant-based interventions for cancer prevention and therapy.

5 Metabolic Reprogramming in Cancer

5.1 Metabolic Pathways in Cancer Cells

Cancer cells undergo extensive metabolic reprogramming to fulfill their increased energy and biosynthetic demands necessary for rapid proliferation and survival. Key pathways such as glycolysis, lipid, and amino acid metabolism are notably altered [19]. The Warburg effect, a hallmark of cancer metabolism, involves cancer cells favoring glycolysis for ATP production even in oxygen-rich conditions, leading to increased glucose uptake and lactate production [15]. This shift not only supports rapid cell growth but also contributes to an acidic tumor microenvironment, promoting invasive behavior and metastasis [52, 53, 54, 55, 56].

Alterations in lipid metabolism, characterized by enhanced lipogenesis and lipid accumulation, provide energy reserves and support membrane biosynthesis [57]. The tumor microenvironment's hypoxia and nutrient deprivation drive these adaptations, enabling cancer cells to thrive under adverse conditions [57]. Amino acids serve as critical components in cancer metabolism, impacting cell growth and survival, which suggests that dietary restrictions on specific amino acids could be a therapeutic strategy [14]. The tumor microenvironment significantly influences cancer metabolism, with factors like hypoxia and nutrient competition shaping these pathways [18]. Mitochondrial dysfunction and mitophagy are pivotal in tumor development, necessitating a comprehensive understanding of cancer cells' metabolic adaptations [58].

The modularity of metabolic gene networks has been linked to cancer prognosis, such as in hepatocellular carcinoma, indicating potential biomarkers and therapeutic targets [28]. Understanding interactions between metabolic pathways and cancer biology is crucial for developing therapies that exploit cancer cells' metabolic vulnerabilities [28].

5.2 Nutrient Uptake and Utilization

Cancer cells adapt metabolically to survive and proliferate within the tumor microenvironment, characterized by hypoxia and limited nutrients. This includes enhanced metabolic plasticity for efficient nutrient utilization and environmental reshaping to support growth. Cancer cells often increase de novo fatty acid synthesis for membrane biogenesis and energy production, which enhances resilience against metabolic stresses. Interactions with stromal components, such as cancer-associated fibroblasts, further influence this metabolic landscape, presenting therapeutic targets [53, 55, 59, 60].

A key aspect of nutrient reprogramming is increased glucose and glutamine uptake, critical for energy and biosynthesis. The Warburg effect epitomizes this metabolic shift, favoring aerobic glycolysis over oxidative phosphorylation despite adequate oxygen. Lipid metabolism's role in cancer is complex, with studies highlighting the importance of lipid biosynthesis and accumulation in tumor growth and metastasis [59]. Research inconsistencies due to varied methods and conditions emphasize the need for standardized approaches [59].

The tumor microenvironment shapes cancer metabolism, with hypoxia and nutrient availability influencing adaptations [58]. Nutrient competition within the TME drives reprogramming, enabling cancer cells to outcompete normal cells for nutrients, creating a hostile environment for immune cells [27]. This competition is crucial in cancer progression, fostering adaptations that promote growth and therapy resistance [27].

The Cancer Metabolism Gene Signature (CMGS) encapsulates cellular metabolism and growth interactions, providing a framework for simulating tumor cell behavior [61]. This model emphasizes the dynamic nature of cancer metabolism and its role in tumorigenesis, underscoring the need to understand altered metabolic pathways.

The interplay between tumorigenesis, metabolic reprogramming, and therapy highlights the importance of strategies targeting cancer cells' metabolic vulnerabilities [62]. Targeting pathways critical for survival, such as glycolysis and lipid metabolism, may enhance treatment efficacy [10].

5.3 Metabolic Vulnerabilities and Therapeutic Strategies

Metabolic vulnerabilities offer critical targets for cancer treatment, as they are essential for cancer cell survival and proliferation. Cancer cells reprogram metabolism to meet increased energy and biosynthetic demands for rapid growth [62], featuring enhanced glycolysis, glutaminolysis, and lipid biosynthesis, collectively supporting tumor growth and metastasis [10].

The Warburg effect represents a key vulnerability, with cancer cells preferring aerobic glycolysis, leading to increased glucose uptake and lactate production despite oxygen presence [15]. This shift, driven by pathways like ERK and JNK, also contributes to therapy resistance [15]. Targeting these pathways offers a strategy to selectively disrupt cancer growth while sparing normal cells [5].

SIRT6 regulation of apoptosis and nutrient deprivation illustrates the complex interactions between metabolism and cancer survival [25]. As a sirtuin family member, SIRT6 regulates responses to nutrient deprivation and oxidative stress, crucial in cancer development.

Reactive oxygen species (ROS) present both challenges and opportunities for therapy. While ROS can promote tumorigenesis through mutations and pro-tumorigenic pathways, they can be targeted to enhance treatment effectiveness [3]. Developing therapies that exploit metabolic vulnerabilities, including ROS and inflammasomes, represents a promising avenue for improving outcomes [5].

Metabolic competition between cancer and immune cells within the tumor microenvironment affects therapy efficacy [27]. This competition drives adaptations promoting growth and therapy resistance, making it crucial to understand these interactions for effective strategies targeting metabolic vulnerabilities while enhancing conventional therapies.

6 Targeted Therapy and Nutrient Metabolism

Category	Feature	Method
Metabolic Vulnerabilities and Therapeutic Strategies	Nutrient-Based Strategies	CMP[25]

Table 1: This table summarizes the methods employed in exploiting metabolic vulnerabilities and therapeutic strategies in cancer treatment. It highlights nutrient-based strategies, specifically referencing the use of CMP as a method, which is crucial for understanding the integration of metabolic reprogramming in targeted therapies.

The integration of targeted therapies in cancer treatment focuses on exploiting specific molecular and metabolic pathways dysregulated in cancer cells to enhance therapeutic efficacy. Table 3 provides an overview of the methods used to exploit metabolic vulnerabilities in cancer cells, focusing on nutrient-based strategies as a key component of targeted therapy approaches. Additionally, Table 2 presents a detailed comparison of different methods in targeted cancer therapy, emphasizing the exploitation of metabolic vulnerabilities and the integration of antioxidants. This approach includes metabolic reprogramming and personalized dietary interventions, aiming to minimize damage to normal tissues through strategies like amino acid restriction and precision oncology techniques targeting molecular alterations [8, 6, 14, 10]. Understanding the mechanisms underlying targeted therapy involves examining the intricate relationship between these therapies and metabolic pathways, which is crucial for improving treatment outcomes and identifying metabolic pathways suitable for therapeutic targeting.

6.1 Targeted Therapy and Metabolic Pathways

Targeted therapy is a pivotal strategy in cancer treatment, focusing on modulating specific molecular and metabolic pathways disrupted in cancer cells. Tumor heterogeneity, characterized by genetic alterations and metabolic reprogramming, necessitates precision oncology to inhibit dysregulated pathways involving growth factors, oncogenes, and tumor suppressor genes. The dynamic nature of cancer metabolism, marked by metabolic plasticity, requires tailored interventions that adapt to cancer cells' evolving demands. Advances in drug discovery, particularly targeting ubiquitination processes and lipid metabolism pathways, highlight the potential for innovative treatments addressing tumorigenesis and progression [8, 63, 57, 10]. The Warburg effect, a hallmark of cancer metabolism, involves a reliance on glycolysis for energy production, even with oxygen, driven by signaling pathways such as ERK and JNK, which are implicated in resistance to chemotherapy and radiotherapy [15]. Targeting these pathways offers a promising strategy to selectively disrupt cancer cell growth while sparing normal cells [5].

Exploiting metabolic vulnerabilities in cancer cells is promising for targeted therapy, as these vulnerabilities arise from adaptations necessary for survival in the tumor microenvironment. Adaptations like upregulation of glycolysis, glutaminolysis, and lipid biosynthesis facilitate rapid proliferation by providing resources for membrane biogenesis and energy production. The reliance on lipid metabolism, particularly through fatty acid synthase (FASN), is crucial for sustaining cancer cell growth under metabolic stress, influencing their response to therapies [59, 60]. Phytochemicals, naturally occurring compounds in plants, show promise in targeting multiple molecular pathways involved in carcinogenesis, complementing traditional cancer therapies [26]. Additionally, antioxidants have potential in targeted therapy strategies due to their role in modulating oxidative stress pathways, enhancing therapeutic effects [5].

6.2 Therapeutic Targeting of Metabolic Pathways

Therapeutic targeting of metabolic pathways in cancer cells is a promising strategy for effective treatments. The distinctive metabolic reprogramming in cancer cells reveals critical vulnerabilities for intervention. This reprogramming involves enhanced glycolysis, glutaminolysis, and lipid biosynthesis, supporting rapid tumor growth. Understanding these altered processes allows identification of molecular targets for innovative treatments [52, 64, 57]. Inhibiting key enzymes in cancer cell metabolism, such as SIRT6, which regulates apoptosis and nutrient deprivation, underscores the potential for targeting pathways to disrupt cancer cell survival [25]. The Warburg effect, characterized by glycolysis preference, driven by ERK and JNK pathways, represents another therapeutic target [15].

The interaction between cancer cells and the tumor microenvironment presents another therapeutic avenue. Metabolic competition between cancer and immune cells impacts immune response against tumors, presenting a target for therapeutic strategies [27]. Disrupting cancer cells' metabolic dependencies while enhancing immune cells' metabolic fitness may improve therapy efficacy and overcome resistance mechanisms. Targeted therapies exploiting cancer cells' metabolic vulnerabilities represent a promising frontier, focusing on specific pathways like glycolysis and lipid metabolism, improving patient outcomes while minimizing side effects [8, 19, 57, 10].

6.3 Integrating Antioxidants into Targeted Therapy

Integrating antioxidants into targeted cancer therapy regimens enhances treatment efficacy and reduces adverse effects. Oxidative stress's dual role in cancer, promoting tumorigenesis while serving as a therapeutic target, underscores antioxidants' potential in targeted therapy [5]. Antioxidants, especially polyphenols, enhance conventional cancer treatments by neutralizing free radicals and reducing oxidative stress [39]. These compounds, found in plant-based foods, mitigate oxidative damage, potentially improving treatment outcomes and reducing side effects.

Antioxidants' integration into therapy regimens is supported by their ability to modulate signaling pathways involved in cancer cell growth and survival. Their interaction with pathways like ERK and JNK, implicated in cancer progression and resistance, highlights potential to enhance targeted therapies' efficacy [15]. By disrupting these pathways, antioxidants may help overcome resistance mechanisms and improve overall treatment effectiveness. Antioxidants' role in modulating the tumor microenvironment is an active research area, significantly influencing cancer progression and response to therapy [18]. By reducing oxidative stress and modulating immune function within the tumor microenvironment, antioxidants may enhance targeted therapies' efficacy, contributing to a holistic cancer treatment approach.

6.4 Metabolic Vulnerabilities and Therapeutic Strategies

Cancer cells exhibit distinct metabolic reprogramming, prominently characterized by the Warburg effect, which supports rapid proliferation and survival. This adaptation involves a preference for aerobic glycolysis over oxidative phosphorylation, facilitating increased glucose uptake and lactate production to meet heightened energy and biosynthetic demands [15]. A primary metabolic vulnerability is reliance on specific nutrients such as glucose and glutamine. The Warburg effect illustrates tumor cells' metabolic dependency, contributing to an acidic tumor microenvironment, supporting tumor growth and enhancing invasive behavior and metastasis. The interplay between tumor metabolism and the microenvironment, including nutrient availability and cancer-associated fibroblasts, critically shapes these processes, influencing progression and therapeutic outcomes [53, 65, 60]. Targeting these pathways offers a promising strategy, as disrupting glycolysis and glutaminolysis can impair cancer cell viability while sparing normal cells.

Lipid metabolism plays a crucial role in cancer survival, with increased lipogenesis supporting membrane biosynthesis and providing energy reserves [57]. The tumor microenvironment, often characterized by hypoxia and nutrient deprivation, influences these adaptations, driving cancer cells to optimize metabolic pathways for survival [57]. Innovative strategies aim to exploit these vulnerabilities. Dietary restriction of specific amino acids has been proposed to inhibit growth, leveraging nutritional dependencies to enhance treatment outcomes [14]. Targeting SIRT6's regulatory role in apoptosis and nutrient deprivation underscores potential for manipulating pathways to improve efficacy [25]. The microenvironment significantly influences metabolism, with nutrient competition between cancer and immune cells impacting responses [18]. Understanding this interplay is crucial for effective therapies, as it affects the immune system's ability to target tumors [27]. Targeting macropinocytosis, a nutrient acquisition pathway, presents a novel therapeutic avenue [66]. The roles of YAP/TAZ as critical nodes in metabolism further highlight potential targets for metabolism-related cancers, offering new strategies [67].

7 Targeted Therapy and Nutrient Metabolism

The integration of targeted therapy and nutrient metabolism in cancer treatment has emerged as a pivotal research area. Targeted therapy aims to enhance treatment efficacy by focusing on specific

Feature	Targeted Therapy and Metabolic Pathways	Therapeutic Targeting of Metabolic Pathways	Integrating Antioxidants into Targeted Therapy
Focus Area	Cancer Metabolism	Metabolic Vulnerabilities	Oxidative Stress
Key Mechanism	Metabolic Reprogramming	Enzyme Inhibition	Free Radical Neutralization
Therapeutic Strategy	Pathway Inhibition	Targeted Interventions	Antioxidant Integration

Table 2: This table offers a comprehensive comparison of three approaches in targeted cancer therapy, focusing on metabolic pathways and oxidative stress. It highlights the distinct focus areas, key mechanisms, and therapeutic strategies associated with each method, providing insights into their roles in cancer treatment.

Category	Feature	Method
Metabolic Vulnerabilities and Therapeutic Strategies	Nutrient-Based Strategies	CMP[25]

Table 3: This table summarizes the methods employed in exploiting metabolic vulnerabilities and therapeutic strategies in cancer treatment. It highlights nutrient-based strategies, specifically referencing the use of CMP as a method, which is crucial for understanding the integration of metabolic reprogramming in targeted therapies.

molecular pathways, thereby minimizing harm to healthy cells. A comprehensive understanding of the metabolic alterations in cancer cells, characterized by unique nutrient dependencies and metabolic reprogramming, is essential for this approach. The following subsection explores the intricate relationship between targeted therapy and metabolic pathways, emphasizing how these pathways can be strategically exploited to improve therapeutic outcomes and address challenges posed by cancer's metabolic adaptations.

7.1 Targeted Therapy and Metabolic Pathways

Targeted therapy has transformed cancer treatment by concentrating on specific molecular and metabolic pathways that are often dysregulated in cancer cells, potentially improving outcomes while minimizing damage to normal cells [55]. A critical aspect of this approach is leveraging the unique metabolic reprogramming in cancer cells, characterized by heightened glycolysis, glutaminolysis, and lipid biosynthesis [68]. These pathways are vital for meeting the increased energy and biosynthetic demands of rapidly proliferating tumors.

Recent research underscores the significance of targeting metabolic pathways in both cancer and immune cells, as this dual strategy can enhance immunotherapy efficacy [27]. By integrating therapies that address the metabolic needs of both cancer and immune cells, overall treatment effectiveness can be improved, potentially overcoming resistance mechanisms.

The modularity of metabolic gene networks, particularly in hepatocellular carcinoma (HCC), provides a novel framework for assessing cancer aggressiveness and developing prognostic tools [28]. Understanding these networks enables the identification of key metabolic vulnerabilities for therapeutic targeting, thereby enhancing treatment strategies.

Additionally, the role of ubiquitination pathways in cancer metabolism presents opportunities for novel therapeutic strategies by disrupting regulatory mechanisms that support cancer cell survival and proliferation [63]. This highlights the potential of targeting post-translational modifications to interfere with cancer metabolism.

Precision oncology, which merges genomic analysis with treatment development and clinical application, is vital for advancing targeted therapies [8]. Tailoring treatments to the genetic and metabolic profiles of individual tumors can enhance efficacy and reduce adverse effects.

7.2 Therapeutic Targeting of Metabolic Pathways

Targeting metabolic pathways in cancer cells offers a promising strategy for developing effective treatments by exploiting their unique metabolic adaptations. A key target is glutaminase, an enzyme critical for cancer metabolism. The development of specific inhibitors like CB-839 for glutaminase underscores the potential of targeting glutamine metabolism in cancer therapy [68]. This strategy aims to disrupt glutamine supply, a vital nutrient for many cancer cells, thereby hindering their growth.

Combining metabolic inhibitors with conventional treatments provides a strategic advantage in overcoming resistance and improving outcomes. The relationship between metabolism and immune response is crucial, as understanding these interactions can inform therapies that target both cancer and immune cell metabolism [62]. Such combinations can enhance the efficacy of cancer therapies and address tumor adaptive capabilities [10].

The ERK and JNK pathways are significant in the therapeutic targeting of metabolic processes. Targeting the ERK pathway may enhance glycolysis in tumors, while activating the JNK pathway could suppress glycolysis and promote apoptosis in glycolytic cancers [15]. These pathways represent potential targets for interventions disrupting the metabolic processes that sustain cancer cell survival.

Lipid metabolism is another critical area for intervention. Sterol regulatory element-binding proteins (SREBPs) are key regulators of lipid metabolism in cancer, with specific inhibitors available for therapeutic targeting [57]. Disrupting lipid biosynthesis and accumulation aims to impair tumor growth by affecting membrane formation and energy storage.

Furthermore, the transcription factor E4F1 has emerged as a potential target, particularly in p53-deficient tumors [69]. Targeting E4F1 could provide a novel therapeutic approach tailored to specific genetic profiles.

The integration of artificial intelligence in treatment planning and ongoing genomic profiling research is essential for advancing precision oncology [8]. These technologies enable the tailoring of metabolic therapies to the unique characteristics of individual tumors, enhancing treatment precision and efficacy.

7.3 Integrating Antioxidants into Targeted Therapy

Integrating antioxidants into targeted cancer therapy presents a promising strategy to enhance efficacy and mitigate side effects of conventional treatments. Antioxidants counteract oxidative stress by neutralizing reactive oxygen species (ROS), which are often produced excessively during cancer progression and treatment. This ROS overproduction can lead to cellular damage and tumorigenesis, as oxidative stress disrupts the balance between ROS and antioxidant defenses. Understanding the dual roles of ROS—as contributors to cancer and potential mediators of cell signaling—highlights the complexity of targeting oxidative stress in cancer therapies [5, 11, 42].

Recent research emphasizes the potential of antioxidants, particularly polyphenols, in enhancing the efficacy of conventional cancer treatments [39]. These compounds, found in various plant-based foods, possess potent antioxidant properties that can neutralize free radicals and reduce oxidative stress [39]. By mitigating oxidative damage, antioxidants may improve the therapeutic effects of targeted therapies, enhancing outcomes and reducing side effects [40].

The integration of antioxidants into targeted regimens is further supported by their ability to modulate key signaling pathways involved in cancer cell growth and survival, such as ERK and JNK, which are implicated in chemotherapy and radiotherapy resistance [15]. The dual role of oxidative stress in cancer, where it can promote tumorigenesis and serve as a therapeutic target, underscores the potential of antioxidants in enhancing targeted interventions [5].

Moreover, antioxidants may influence the tumor microenvironment, which significantly impacts cancer progression and therapy response [18]. By reducing oxidative stress and modulating immune function within the tumor microenvironment, antioxidants could enhance the efficacy of targeted therapies, contributing to a more holistic approach to cancer treatment.

7.4 Interplay Between Nutrient Metabolism and Cancer Microenvironment

The relationship between nutrient metabolism and the tumor microenvironment is crucial in cancer progression and therapy resistance. Characterized by hypoxia, nutrient scarcity, and metabolic competition, the tumor microenvironment significantly influences cancer cell metabolism, driving metabolic reprogramming and adaptation [58]. Understanding this interplay is essential for elucidating the biological processes underlying tumorigenesis and developing effective cancer therapies.

The unique conditions of the tumor microenvironment, including hypoxia, nutrient deprivation, and ROS presence, collectively influence cancer cell metabolism and behavior. Hypoxia, common in tumors, drives metabolic reprogramming, promoting glycolysis and other pathways that support

tumor growth and survival [62]. This adaptation enables cancer cells to thrive in nutrient-scarce and low-oxygen conditions, contributing to tumor progression and metastasis [57].

Nutrient competition within the tumor microenvironment is a critical factor in cancer progression. Cancer and immune cells compete for essential nutrients, such as glucose and amino acids, vital for their survival and function [27]. This competition can lead to metabolic adaptations that enhance cancer cell growth while impairing the immune system's ability to mount an effective response against the tumor [27].

ROS and oxidative stress are key elements in the tumor microenvironment, influencing both cancer progression and therapy efficacy. ROS can promote tumorigenesis by inducing genetic mutations and activating pro-tumorigenic signaling pathways, while also serving as therapeutic targets to enhance treatment effectiveness. The interactions between ROS, nutrient metabolism, and cancer biology are critical for developing effective therapeutic strategies [41].

Hypoxia further complicates the interplay between nutrient metabolism and cancer progression. Under hypoxic conditions, cancer cells undergo metabolic reprogramming, often resulting in increased glycolysis and lactate production. This shift not only supports tumor growth but also creates an acidic microenvironment conducive to invasion and metastasis [17].

The multifaceted role of ROS in the tumor microenvironment, where they can promote both tumorigenesis and therapeutic targeting, emphasizes the need for a nuanced understanding of their interactions with nutrient metabolism and cancer biology [5]. Antioxidants, by neutralizing ROS and reducing oxidative stress, may offer complementary strategies to conventional cancer therapies, especially within the tumor microenvironment [46].

7.5 Influence of Tumor Microenvironment on Nutrient Metabolism

The tumor microenvironment significantly influences nutrient metabolism, playing a critical role in cancer progression and therapy resistance. Characterized by hypoxia, nutrient scarcity, and ROS, this dynamic environment drives metabolic reprogramming in cancer cells. The interplay between the tumor microenvironment and nutrient metabolism dictates the metabolic adaptations of cancer cells, influencing their proliferation, behavior, and resistance to therapies. The TME, shaped by interactions among cancer and surrounding non-malignant cells, creates a unique niche affecting nutrient availability and metabolic reprogramming [53, 65, 60, 54].

Hypoxia, a defining feature of the tumor microenvironment, plays a crucial role in shaping cancer cell metabolism. Under low oxygen conditions, cancer cells increasingly rely on glycolysis for energy, a phenomenon known as the Warburg effect [62]. This metabolic shift allows cancer cells to sustain energy production and biosynthesis despite insufficient oxygen, supporting rapid growth and survival [10]. The resultant acidic microenvironment from increased lactate production further promotes invasion and metastasis [17].

Nutrient scarcity within the tumor microenvironment drives metabolic adaptations, enabling cancer cells to outcompete normal cells for essential nutrients like glucose and amino acids [27]. This competition significantly impacts the immune response against tumors, as immune cells also depend on these nutrients for their function and survival. The metabolic competition between cancer and immune cells underscores the need for therapeutic strategies that target the unique metabolic dependencies of cancer cells while preserving immune cell fitness [27].

Additionally, the tumor microenvironment is marked by high levels of ROS, which can induce oxidative stress and contribute to cancer progression [5]. The dual role of ROS in cancer biology—promoting tumorigenesis and serving as therapeutic targets—highlights the importance of understanding their interactions with nutrient metabolism. Antioxidants, by neutralizing ROS and reducing oxidative stress, may enhance conventional cancer therapies, improving efficacy and minimizing side effects [46].

7.6 Nutrient Competition and Metabolic Adaptations

The tumor microenvironment is defined by nutrient competition and metabolic adaptations that play critical roles in cancer progression and therapy resistance. Cancer and immune cells compete for essential nutrients, such as glucose and amino acids, vital for their survival and function [27]. This

competition drives metabolic reprogramming in cancer cells, allowing them to outcompete normal cells for resources and creating a hostile environment for immune cells.

A key metabolic adaptation in cancer cells is the Warburg effect, characterized by a preference for glycolysis for energy production, even in the presence of oxygen. This metabolic shift enables cancer cells to rapidly generate ATP and biosynthetic precursors essential for proliferation and survival, while also contributing to an acidic tumor microenvironment that promotes invasion and metastasis [15].

The role of SIRT6 in regulating apoptosis and nutrient deprivation further emphasizes the complex interactions between metabolic pathways and cancer cell survival [25]. SIRT6, a member of the sirtuin family, regulates cellular responses to nutrient deprivation and oxidative stress, key factors in cancer development and progression.

The tumor microenvironment's impact on cancer metabolism is complicated by ROS presence, which influences both cancer progression and therapy resistance. ROS can induce oxidative stress, a critical factor in cancer pathogenesis, by causing DNA damage and activating pro-tumorigenic signaling pathways. However, ROS also represent potential therapeutic targets, as their modulation can enhance the efficacy of cancer treatments [5].

7.7 Role of Reactive Oxygen Species (ROS) and Antioxidants

Reactive oxygen species (ROS) and antioxidants are central to the interplay between nutrient metabolism and the tumor microenvironment, significantly influencing cancer progression and therapy outcomes. Generated as byproducts of metabolic processes, ROS play a dual role in tumorigenesis by inducing oxidative stress, disrupting the balance between ROS production and the body's antioxidant defenses. This oxidative stress can lead to cellular damage, including DNA mutations and protein oxidation, contributing to cancer initiation and progression. Dysregulated ROS levels can activate oncogenic signaling pathways, promote angiogenesis and metastasis, and influence the tumor microenvironment, making oxidative stress modulation a potential therapeutic strategy [5, 11, 3].

Antioxidants, which neutralize free radicals and reduce oxidative stress, play a crucial role in modulating ROS effects within the tumor microenvironment [46]. By mitigating oxidative damage, antioxidants can help prevent genetic mutations and signaling pathway activations that contribute to cancer development [39]. However, the dual role of antioxidants as protective agents and potential pro-oxidants complicates their study in cancer biology, necessitating a nuanced understanding of their activity in different contexts.

The tumor microenvironment, characterized by hypoxia and nutrient competition, significantly influences ROS production and activity, impacting cancer cell metabolism and immune function. The interplay between ROS and the tumor microenvironment is a critical research area, as it can significantly affect cancer progression and therapy efficacy [5]. Understanding the interactions between ROS, oxidative stress, and the tumor microenvironment is essential for developing effective therapeutic strategies targeting cancer metabolic vulnerabilities and enhancing treatment outcomes.

Moreover, ongoing research focuses on developing advanced antioxidants with improved bioavailability and efficacy, as these compounds hold significant potential for cancer prevention and therapy [40]. Optimizing antioxidant structural characteristics, such as hydroxyl groups and metal complexation capabilities, aims to enhance their properties and therapeutic potential [40].

7.8 Impact of Hypoxia and Oxidative Stress

Hypoxia and oxidative stress are critical factors significantly influencing nutrient metabolism and cancer progression within the tumor microenvironment. Hypoxia, resulting from insufficient oxygen supply, drives metabolic reprogramming in cancer cells [62]. Under hypoxic conditions, cancer cells often favor aerobic glycolysis, known as the Warburg effect, enabling them to maintain energy production and biosynthesis despite limited oxygen availability.

The Warburg effect, characterized by increased glucose uptake and lactate production, supports rapid cancer cell proliferation and contributes to an acidic tumor microenvironment. This acidic environment can promote tumor invasion and metastasis, complicating cancer treatment [15]. Understanding

the interplay between hypoxia, oxidative stress, and nutrient metabolism is crucial for developing effective therapeutic strategies targeting cancer metabolic vulnerabilities.

ROS, byproducts of metabolic processes, play a dual role in cancer biology. While they can induce oxidative stress and promote tumorigenesis by causing DNA damage and activating pro-tumorigenic signaling pathways, ROS can also be targeted therapeutically to enhance cancer treatment effectiveness [5]. The role of ROS in cancer underscores the importance of understanding the interactions between oxidative stress, nutrient metabolism, and the tumor microenvironment in developing effective therapies [3].

The tumor microenvironment (TME), characterized by hypoxia and nutrient competition, modulates ROS production and activity, significantly affecting cancer cell metabolism and immune function. The TME influences how tumor cells adapt their metabolic processes to thrive under stress and interact with surrounding stromal cells. Dysregulated ROS levels within the TME can lead to enhanced tumor progression, immune evasion, and metastasis, highlighting the complex interplay between the TME and cancer biology [53, 5, 54, 11, 3]. The interplay between hypoxia, oxidative stress, and nutrient metabolism is critical for understanding cancer progression and therapy resistance, emphasizing the need for developing effective strategies targeting cancer metabolic vulnerabilities to improve treatment outcomes.

8 Interplay Between Nutrient Metabolism and Cancer Microenvironment

The intricate relationship between nutrient metabolism and the tumor microenvironment (TME) is shaped by microenvironmental factors such as nutrient availability and interstitial fluid composition, which influence tumor behavior and progression [53, 60]. The TME modulates nutrient metabolism through its cellular components and their metabolic demands, pivotal for cancer progression and therapeutic responses.

8.1 Influence of Tumor Microenvironment on Nutrient Metabolism

Characterized by hypoxia, limited nutrients, and diverse cellular composition, the TME affects cancer cell metabolism significantly. Cancer-associated fibroblasts (CAFs) and immune cells within the TME influence tumor growth dynamics and therapy responses [60, 53, 70, 56, 71]. Hypoxia, due to inadequate blood supply, leads to metabolic reprogramming, increasing glycolysis and lactate production, fostering an acidic TME that supports tumor invasion and survival under stress [53, 55]. Cancer cells exhibit metabolic plasticity, utilizing glucose and glutamine for proliferation.

Neutrophils adapt by engaging in oxidative mitochondrial metabolism, maintaining immune suppression in nutrient-limited conditions [72]. Nutrient competition, particularly for glucose and glutamine, between cancer and immune cells, affects progression and therapy resistance [71], impairing T cells and NK cells reliant on these nutrients for antitumor activity [27]. ROS in the TME have dual roles, inducing genetic mutations and activating pathways, yet also serving as therapeutic targets [5]. Exosomes further complicate metabolic pathways and progression [73]. Neutrophils' metabolic adaptations highlight their role in immune suppression and tumor progression, emphasizing the need to understand TME, nutrient metabolism, and immune interactions for effective therapies [70].

8.2 Nutrient Competition and Metabolic Adaptations

Within the TME, cancer, immune, and stromal cells compete for scarce resources, crucially influencing nutrient metabolism and metabolic adaptations. This competition leads to cancer cell reprogramming, allowing them to outcompete normal cells for resources, creating a hostile environment for immune cells [70]. Wnt signaling affects nutrient metabolism, modulating metabolite availability and utilization, influencing metabolic adaptations [74]. Toxic metabolites like lactate suppress immune function, promoting tumor growth and creating an acidic microenvironment favoring cancer survival [70].

Tumor-stromal cell interactions drive metabolic changes supporting tumor growth [54]. CAFs provide metabolic support through nutrient and growth factor secretion, enhancing cancer survival via reprogramming [54]. Understanding these interactions and metabolite utilization mechanisms is a significant challenge in cancer research [54].

8.3 Role of Reactive Oxygen Species (ROS) and Antioxidants

ROS and antioxidants are critical in the TME, affecting cancer development, progression, and therapeutic outcomes. ROS function as signaling molecules and damage sources, with complex roles in cancer biology [47]. Within the TME, ROS levels correlate with cancer stages, influencing initiation, promotion, and therapy responses [38]. Modulating ROS can have context-dependent effects, with pro- and anti-tumorigenic outcomes based on tumor type and conditions [11].

Antioxidants, including enzymes, diet-derived compounds, and repair mechanisms, maintain cellular homeostasis by neutralizing ROS and preventing damage [49]. The interplay between ROS and the TME is multifaceted, as high ROS levels can induce oxidative stress, leading to DNA damage and tumorigenesis, while also triggering oxidative damage that suppresses tumor growth [5]. The metabolic dynamics of glucose consumption by tumor-infiltrating myeloid cells, exceeding that of T cells or cancer cells, complicates the roles of ROS and antioxidants [71]. Understanding these dynamics is crucial for developing cancer therapies.

8.4 Impact of Hypoxia and Oxidative Stress

Hypoxia and oxidative stress within the TME significantly impact nutrient metabolism, affecting cancer progression and treatment resistance. Hypoxia, common in solid tumors due to oxygen imbalance, drives metabolic reprogramming, leading cancer cells to rely on anaerobic glycolysis for ATP, creating an acidic microenvironment that promotes invasion and metastasis [18, 62, 15]. Hypoxia influences ROS production, which can promote tumorigenesis through mutations and signaling pathways or suppress growth via oxidative damage [47, 5].

The hypoxic TME modulates ROS production, affecting cancer metabolism and immune function. The competition for nutrients leads to metabolic adaptations, enabling cancer cells to outcompete normal cells, complicating treatment strategies [27]. Understanding hypoxia, oxidative stress, and nutrient metabolism interactions is essential for developing effective cancer therapies.

9 Conclusion

9.1 Therapeutic Implications and Future Directions

The complex interactions among vitamins, antioxidants, nutrient metabolism, and the tumor microenvironment (TME) offer significant insights for advancing cancer therapy and prevention. These elements collectively influence cancer progression and therapeutic resistance, underscoring the need for integrated research approaches in cancer biology.

Vitamins such as B, D, and E are crucial for immune regulation and reducing cancer risk. Vitamin B supports immune cell function, potentially lowering cancer severity, while Vitamin D's immunomodulatory properties are vital for both cancer prevention and treatment. Future research should focus on refining methods for measuring vitamin D metabolites to unlock their therapeutic potential.

Antioxidants, notably polyphenols, show promise in reducing oxidative stress and modulating cancer-related signaling pathways. Their dual role as both protective agents and potential pro-oxidants requires careful investigation to optimize their use in cancer therapy. Ongoing research aims to enhance antioxidant bioavailability and efficacy, expanding their therapeutic applications.

The TME, characterized by hypoxia and nutrient competition, significantly impacts cancer progression and resistance to treatment. Understanding the metabolic crosstalk between cancer and immune cells within the TME is crucial for developing targeted metabolic therapies. Reactive oxygen species (ROS) and oxidative stress add complexity to cancer dynamics, offering both challenges and opportunities for therapeutic targeting.

Phytochemicals, including polyphenols and flavonoids, have shown potential in cancer prevention and treatment by engaging multiple carcinogenic pathways. These compounds can target cancer stem cells and modify the TME, crucial for inhibiting tumor growth and metastasis. Integrating natural compounds into targeted therapies could improve outcomes by addressing metabolic and molecular disruptions in cancer cells.

ROS and antioxidants present both therapeutic challenges and opportunities. While ROS can drive tumorigenesis through mutations and signaling, they also serve as potential therapeutic targets. Antioxidants may complement conventional therapies by neutralizing ROS, enhancing treatment effectiveness, and reducing side effects.

Targeted therapies exploiting cancer cells' metabolic vulnerabilities offer promising avenues for improving treatment outcomes. By focusing on specific molecular and metabolic abnormalities, these therapies aim to selectively disrupt cancer cell growth while preserving normal cells. Incorporating natural compounds into these strategies may enhance their efficacy by affecting multiple carcinogenic pathways.

Advancing measurement techniques for vitamin D metabolites and exploring their pharmacological roles are essential for understanding vitamin D's impact on cancer biology. Establishing a detailed framework for categorizing vitamin D metabolites will facilitate further exploration of its preventive and therapeutic potential.

References

[1] Paola De Cicco, Maria Valeria Catani, Valeria Gasperi, Matteo Sibilano, Maria Quaglietta, and Isabella Savini. Nutrition and breast cancer: a literature review on prevention, treatment and recurrence. *Nutrients*, 11(7):1514, 2019.

[2] Seongeung Lee, Youngmin Choi, Heon Sang Jeong, Junsoo Lee, and Jeehye Sung. Effect of different cooking methods on the content of vitamins and true retention in selected vegetables. *Food science and biotechnology*, 27:333–342, 2018.

[3] Anuradha Kirtonia, Gautam Sethi, and Manoj Garg. The multifaceted role of reactive oxygen species in tumorigenesis. *Cellular and Molecular Life Sciences*, 77:4459–4483, 2020.

[4] Alicia Martínez-González, Mario Durán-Prado, Gabriel F. Calvo, Francisco J. Alcaín, Luis A. Pérez-Romasanta, and Víctor M. Pérez-García. Combined therapies of antithrombotics and antioxidants delay in silico brain tumor progression, 2014.

[5] Kexin Li, Zhangyuzi Deng, Chunran Lei, Xiaoqing Ding, Jing Li, and Changshan Wang. The role of oxidative stress in tumorigenesis and progression. *Cells*, 13(5):441, 2024.

[6] Francis Heylighen. Cybernetic principles of aging and rejuvenation: the buffering-challenging strategy for life extension, 2014.

[7] Hiroki Nagai and Young Hak Kim. Cancer prevention from the perspective of global cancer burden patterns. *Journal of thoracic disease*, 9(3):448, 2017.

[8] Manish Kumar. Precision oncology, signaling pathways reprogramming and targeted therapy: A holistic approach to molecular cancer therapeutics, 2024.

[9] Wilhelm Palm and Craig B Thompson. Nutrient acquisition strategies of mammalian cells. *Nature*, 546(7657):234–242, 2017.

[10] Sarah-Maria Fendt, Christian Frezza, and Ayelet Erez. Targeting metabolic plasticity and flexibility dynamics for cancer therapy. *Cancer discovery*, 10(12):1797–1807, 2020.

[11] Isaac S Harris and Gina M DeNicola. The complex interplay between antioxidants and ros in cancer. *Trends in cell biology*, 30(6):440–451, 2020.

[12] Christine Tara Peterson, Dmitry A Rodionov, Andrei L Osterman, and Scott N Peterson. B vitamins and their role in immune regulation and cancer. *Nutrients*, 12(11):3380, 2020.

[13] Robert Sotler, Borut Poljšak, Raja Dahmane, Tomislav Jukić, Doroteja Pavan Jukić, Cecilija Rotim, Polonca Trebše, and Andrej Starc. Prooxidant activities of antioxidants and their impact on health. *Acta Clinica Croatica*, 58(4.):726–736, 2019.

[14] Jian-Sheng Kang. Dietary restriction of amino acids for cancer therapy, 2020.

[15] Salvatore Papa, Pui Man Choy, and Concetta Bubici. The erk and jnk pathways in the regulation of metabolic reprogramming. *Oncogene*, 38(13):2223–2240, 2019.

[16] Xavier Michelet, Lydia Dyck, Andrew Hogan, Roisin M Loftus, Danielle Duquette, Kevin Wei, Semir Beyaz, Ali Tavakkoli, Cathriona Foley, Raymond Donnelly, et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. *Nature immunology*, 19(12):1330–1340, 2018.

[17] An-Na Chen, Yan Luo, Yu-Han Yang, Jian-Tao Fu, Xiu-Mei Geng, Jun-Ping Shi, and Jin Yang. Lactylation, a novel metabolic reprogramming code: current status and prospects. *Frontiers in immunology*, 12:688910, 2021.

[18] Logan P Poole and Kay F Macleod. Mitophagy in tumorigenesis and metastasis. *Cellular and molecular life sciences*, 78:3817–3851, 2021.

[19] Fahim Ahmad, Murali Krishna Cherukuri, and Peter L Choyke. Metabolic reprogramming in prostate cancer. *British journal of cancer*, 125(9):1185–1196, 2021.

[20] Qurat ul Ain and M. Iqbal Choudhary. Emerging classes of antioxidant to cancer therapy: a review of clinical and experimental studies, 2020.

[21] Ian Rowland, Glenn Gibson, Almut Heinken, Karen Scott, Jonathan Swann, Ines Thiele, and Kieran Tuohy. Gut microbiota functions: metabolism of nutrients and other food components. *European journal of nutrition*, 57:1–24, 2018.

[22] Vicente Javier Clemente-Suárez, Ana Isabel Beltrán-Velasco, Laura Redondo-Flórez, Alexandra Martín-Rodríguez, and José Francisco Tornero-Aguilera. Global impacts of western diet and its effects on metabolism and health: A narrative review. *Nutrients*, 15(12):2749, 2023.

[23] Sindhu M and Medhavi Vishwakarma. Role of heterogeneity in dictating tumorigenesis in epithelial tissues, 2022.

[24] Zhihong He, Jie He, and Keping Xie. Klf4 transcription factor in tumorigenesis. *Cell death discovery*, 9(1):118, 2023.

[25] Sergii Domanskyi, Justin W. Nicholatos, Joshua E. Schilling, Vladimir Privman, and Sergiy Libert. Sirt6 knockout cells resist apoptosis initiation but not progression: A computational method to evaluate the progression of apoptosis, 2017.

[26] Enrico Catalano. Role of phytochemicals in the chemoprevention of tumors, 2016.

[27] Longzheng Xia, Linda Oyang, Jinguan Lin, Shiming Tan, Yaqian Han, Nayiyuan Wu, Pin Yi, Lu Tang, Qing Pan, Shan Rao, et al. The cancer metabolic reprogramming and immune response. *Molecular cancer*, 20:1–21, 2021.

[28] Fengdan Ye, Dongya Jia, Mingyang Lu, Herbert Levine, and Michael W Deem. Modularity of the metabolic gene network as a prognostic biomarker for hepatocellular carcinoma, 2017.

[29] Hira Shakoor, Jack Feehan, Kathleen Mikkelsen, Ayesha S Al Dhaheri, Habiba I Ali, Carine Platat, Leila Cheikh Ismail, Lily Stojanovska, and Vasso Apostolopoulos. Be well: A potential role for vitamin b in covid-19. *Maturitas*, 144:108–111, 2021.

[30] Indra Ramasamy. Vitamin d metabolism and guidelines for vitamin d supplementation. *The Clinical Biochemist Reviews*, 41(3):103, 2020.

[31] Monica Neagu, Carolina Constantin, Constantin Caruntu, Carmen Dumitru, Mihaela Surcel, and Sabina Zurac. Inflammation: A key process in skin tumorigenesis. *Oncology Letters*, 17(5):4068–4084, 2019.

[32] Ga Young Lee and Sung Nim Han. The role of vitamin e in immunity. *Nutrients*, 10(11):1614, 2018.

[33] Md Sanower Hossain, Md Abdul Kader, Khang Wen Goh, Maidul Islam, Md Sharif Khan, Md Harun-Ar Rashid, Der Jiun Ooi, Henrique Douglas Melo Coutinho, Yaser Mohammed Al-Worafi, Said Moshawih, et al. Herb and spices in colorectal cancer prevention and treatment: A narrative review. *Frontiers in pharmacology*, 13:865801, 2022.

[34] Wei Liu, Lei Zhang, Hui-Jing Xu, Yan Li, Chuan-Min Hu, Jing-Yan Yang, and Mei-Yan Sun. The anti-inflammatory effects of vitamin d in tumorigenesis. *International journal of molecular sciences*, 19(9):2736, 2018.

[35] Ali Reza Yusefi, Kamran Bagheri Lankarani, Peivand Bastani, Maryam Radinmanesh, and Zahra Kavosi. Risk factors for gastric cancer: a systematic review. *Asian Pacific journal of cancer prevention: APJCP*, 19(3):591, 2018.

[36] Ángel Gil, Julio Plaza-Diaz, and María Dolores Mesa. Vitamin d: classic and novel actions. *Annals of Nutrition and Metabolism*, 72(2):87–95, 2018.

[37] Robert C Tuckey, Chloe YS Cheng, and Andrzej T Slominski. The serum vitamin d metabolome: What we know and what is still to discover. *The Journal of steroid biochemistry and molecular biology*, 186:4–21, 2019.

[38] Yawei Wang, Huan Qi, Yu Liu, Chao Duan, Xiaolong Liu, Tian Xia, Di Chen, Hai-long Piao, and Hong-Xu Liu. The double-edged roles of ros in cancer prevention and therapy. *Theranostics*, 11(10):4839, 2021.

[39] Giusi Briguglio, Chiara Costa, Manuela Pollicino, Federica Giambò, Stefania Catania, and Concettina Fenga. Polyphenols in cancer prevention: New insights. *International Journal of Functional Nutrition*, 1(2):9, 2020.

[40] Monika Parcheta, Renata Świsłocka, Sylwia Orzechowska, Monika Akimowicz, Renata Choińska, and Włodzimierz Lewandowski. Recent developments in effective antioxidants: The structure and antioxidant properties. *Materials*, 14(8):1984, 2021.

[41] Charlotte Récapet, Mathilde Arrivé, Blandine Doligez, and Pierre Bize. Antioxidant capacity is repeatable across years but does not consistently correlate with a marker of peroxidation in a free-living passerine bird, 2019.

[42] Bahare Salehi, Miquel Martorell, Jack L Arbiser, Antoni Sureda, Natália Martins, Pawan Kumar Maurya, Mehdi Sharifi-Rad, Pradeep Kumar, and Javad Sharifi-Rad. Antioxidants: positive or negative actors? *Biomolecules*, 8(4):124, 2018.

[43] Dong-Ping Xu, Ya Li, Xiao Meng, Tong Zhou, Yue Zhou, Jie Zheng, Jiao-Jiao Zhang, and Hua-Bin Li. Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International journal of molecular sciences*, 18(1):96, 2017.

[44] Sofia C Lourenço, Margarida Moldão-Martins, and Vítor D Alves. Antioxidants of natural plant origins: From sources to food industry applications. *Molecules*, 24(22):4132, 2019.

[45] Alvaro Juan Ojeda Garcia. Mathematical and computational modeling for describing the basic behavior of free radicals and antioxidants within epithelial cells, 2012.

[46] Cuma Zehiroglu and Sevim Beyza Ozturk Sarikaya. The importance of antioxidants and place in today's scientific and technological studies. *Journal of food science and technology*, 56:4757–4774, 2019.

[47] Klaudia Jomova, Renata Raptova, Suliman Y Alomar, Saleh H Alwasel, Eugenie Nepovimova, Kamil Kuca, and Marian Valko. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. *Archives of toxicology*, 97(10):2499–2574, 2023.

[48] Yiheng Chen, Marek Michalak, and Luis B Agellon. Importance of nutrients and nutrient metabolism on human health. *The Yale journal of biology and medicine*, 91(2):95, 2018.

[49] Klaudia Jomova, Suliman Y Alomar, Saleh H Alwasel, Eugenie Nepovimova, Kamil Kuca, and Marian Valko. Several lines of antioxidant defense against oxidative stress: Antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Archives of Toxicology*, 98(5):1323–1367, 2024.

[50] Priya Chaudhary, Pracheta Janmeda, Anca Oana Docea, Balakyz Yeskaliyeva, Ahmad Faizal Abdull Razis, Babagana Modu, Daniela Calina, and Javad Sharifi-Rad. Oxidative stress, free radicals and antioxidants: Potential crosstalk in the pathophysiology of human diseases. *Frontiers in chemistry*, 11:1158198, 2023.

[51] Balázs Kirschweng, Dóra Tátraaljai, Enikő Földes, and Béla Pukánszky. Natural antioxidants as stabilizers for polymers. *Polymer Degradation and Stability*, 145:25–40, 2017.

[52] Chelsea Schiliro and Bonnie L Firestein. Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. *Cells*, 10(5):1056, 2021.

[53] Miguel Reina-Campos, Jorge Moscat, and Maria Diaz-Meco. Metabolism shapes the tumor microenvironment. *Current opinion in cell biology*, 48:47–53, 2017.

[54] Victoire Gouirand, Fabienne Guillaumond, and Sophie Vasseur. Influence of the tumor microenvironment on cancer cells metabolic reprogramming. *Frontiers in oncology*, 8:117, 2018.

[55] Kenji Ohshima and Eiichi Morii. Metabolic reprogramming of cancer cells during tumor progression and metastasis. *Metabolites*, 11(1):28, 2021.

[56] Hyunkoo Kang, Hyunwoo Kim, Sungmin Lee, HyeSook Youn, and BuHyun Youn. Role of metabolic reprogramming in epithelial–mesenchymal transition (emt). *International Journal of Molecular Sciences*, 20(8):2042, 2019.

[57] Chunming Cheng, Feng Geng, Xiang Cheng, and Deliang Guo. Lipid metabolism reprogramming and its potential targets in cancer. *Cancer communications*, 38:1–14, 2018.

[58] Zhenzhen Li, Chanjun Sun, and Zhihai Qin. Metabolic reprogramming of cancer-associated fibroblasts and its effect on cancer cell reprogramming. *Theranostics*, 11(17):8322, 2021.

[59] Rimsha Munir, Jan Lisec, Johannes V Swinnen, and Nousheen Zaidi. Lipid metabolism in cancer cells under metabolic stress. *British journal of cancer*, 120(12):1090–1098, 2019.

[60] Mark R Sullivan, Laura V Danai, Caroline A Lewis, Sze Ham Chan, Dan Y Gui, Tenzin Kunchok, Emily A Dennstedt, Matthew G Vander Heiden, and Alexander Muir. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *Elife*, 8:e44235, 2019.

[61] Roberto Chignola and Edoardo Milotti. A phenomenological approach to the simulation of metabolism and proliferation dynamics of large tumour cell populations, 2005.

[62] Jinguan Lin, Longzheng Xia, Jiaxin Liang, Yaqian Han, Heran Wang, Linda Oyang, Shiming Tan, Yutong Tian, Shan Rao, Xiaoyan Chen, et al. The roles of glucose metabolic reprogramming in chemo-and radio-resistance. *Journal of Experimental & Clinical Cancer Research*, 38(1):218, 2019.

[63] Lu Deng, Tong Meng, Lei Chen, Wenyi Wei, and Ping Wang. The role of ubiquitination in tumorigenesis and targeted drug discovery. *Signal transduction and targeted therapy*, 5(1):11, 2020.

[64] Marie Strickland and Elizabeth A Stoll. Metabolic reprogramming in glioma. *Frontiers in cell and developmental biology*, 5:43, 2017.

[65] Youness Azimzade, Abbas Ali Saberi, and Muhammad Sahimi. Role of the interplay between the internal and external conditions in invasive behavior of tumors, 2018.

[66] Maria Victoria Recouvreux and Cosimo Commisso. Macropinocytosis: a metabolic adaptation to nutrient stress in cancer. *Frontiers in endocrinology*, 8:261, 2017.

[67] Xiaodong Zhang, Haiying Zhao, Yan Li, Di Xia, Liang Yang, Yingbo Ma, and Hangyu Li. The role of yap/taz activity in cancer metabolic reprogramming. *Molecular cancer*, 17:1–10, 2018.

[68] William P Katt, Michael J Lukey, and Richard A Cerione. A tale of two glutaminases: homologous enzymes with distinct roles in tumorigenesis. *Future medicinal chemistry*, 9(2):223–243, 2017.

[69] Geneviéve Rodier, Olivier Kirsh, Martín Baraibar, Thibault Houlés, Matthieu Lacroix, Héléne Delpech, Elodie Hatchi, Stéphanie Arnould, Dany Severac, Emeric Dubois, Julie Caramel, Eric Julien, Bertrand Friguet, Laurent Le Cam, and Claude Sardet. The transcription factor e4f1 coordinates chk1-dependent checkpoint and mitochondrial functions, 2015.

[70] Robert D Leone and Jonathan D Powell. Metabolism of immune cells in cancer. *Nature reviews cancer*, 20(9):516–531, 2020.

[71] Bradley I Reinfeld, Matthew Z Madden, Melissa M Wolf, Anna Chytil, Jackie E Bader, Andrew R Patterson, Ayaka Sugiura, Allison S Cohen, Ahmed Ali, Brian T Do, et al. Cell-programmed nutrient partitioning in the tumour microenvironment. *Nature*, 593(7858):282–288, 2021.

[72] Christopher M Rice, Luke C Davies, Jeff J Subleski, Nunziata Maio, Marieli Gonzalez-Cotto, Caroline Andrews, Nimit L Patel, Erika M Palmieri, Jonathan M Weiss, Jung-Min Lee, et al. Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression. *Nature communications*, 9(1):5099, 2018.

[73] Enli Yang, Xuan Wang, Zhiyuan Gong, Miao Yu, Haiwei Wu, and Dongsheng Zhang. Exosome-mediated metabolic reprogramming: the emerging role in tumor microenvironment remodeling and its influence on cancer progression. *Signal transduction and targeted therapy*, 5(1):242, 2020.

[74] Yongzhen Mo, Yumin Wang, Lishen Zhang, Liting Yang, Ming Zhou, Xiaoling Li, Yong Li, Guiyuan Li, Zhaoyang Zeng, Wei Xiong, et al. The role of wnt signaling pathway in tumor metabolic reprogramming. *Journal of Cancer*, 10(16):3789, 2019.

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