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Exploring the potential of bioactive compounds in preventing cancer growth and progression: A comprehensive review

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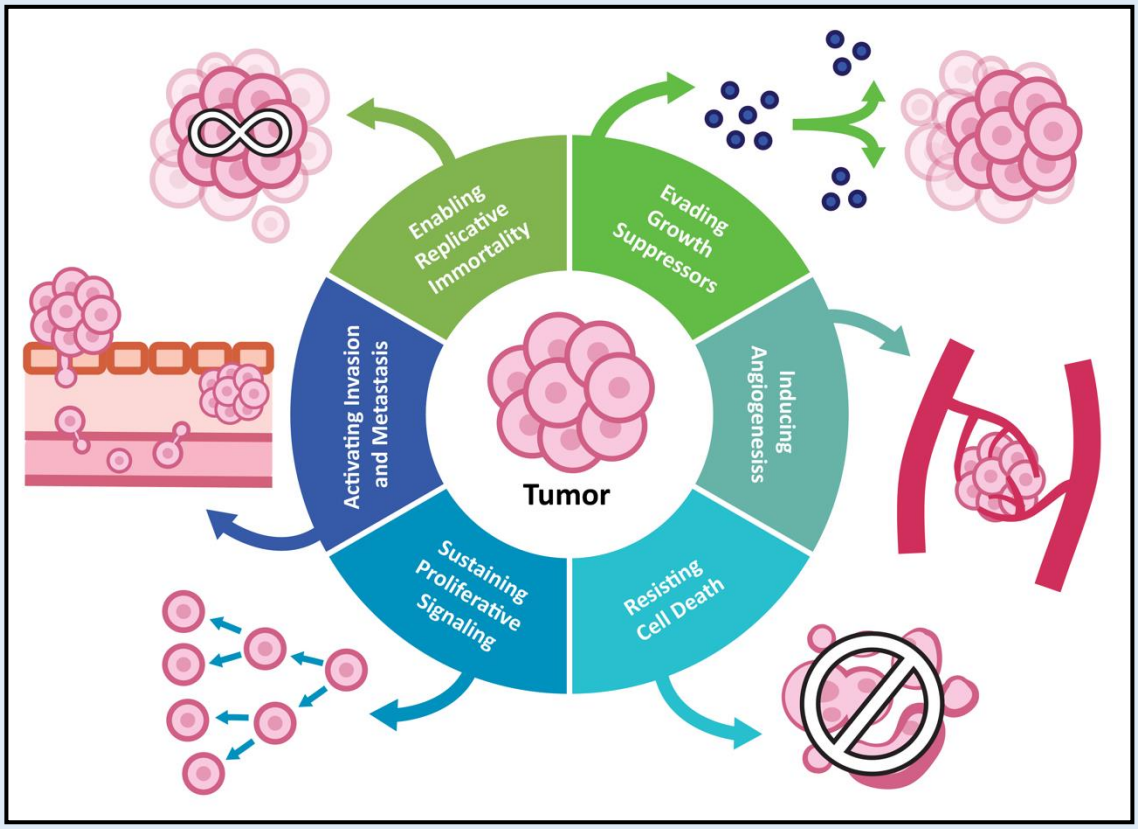
ABSTRACT

Cancer stands as a prominent global cause of mortality, with a noteworthy surge in related deaths in recent years. Over the past decade, several bioactive compounds have emerged as potent agents in impeding the relentless advance of cancer. Notably, numerous studies highlight the efficacy of natural plant-derived bioactive compounds in augmenting chemotherapy outcomes and mitigating adverse drug effects associated with chemotherapeutic agents. This comprehensive review investigates the anticancer effects of three types of bioactive compounds: polyphenols, alkaloids, and terpenoids. It elucidates their mechanisms of action and consolidates evidence from preclinical studies. Furthermore, this review delves into the molecular mechanisms through which these active compounds may manifest their anticancer properties, drawing insights from cell and animal-based studies.

Keywords: Bioactive compounds, cancer prevention, polyphenols, alkaloids, terpenoids



Characteristic traits of tumors that facilitate uncontrolled growth and metastasis

INTRODUCTION

Cancer persists as a formidable global health challenge, casting a significant burden on individuals, families, and healthcare systems worldwide [1]. The rise in cancer cases and the complexity of its progression underscore the urgent need for innovative and effective preventive measures [2]. Amidst the landscape of cancer biology, there is a burgeoning interest in investigating the potential of bioactive compounds sourced from nature as a promising frontier in cancer prevention [3].

Cancers may stem from inflammatory processes triggered by the rapid growth of self-origin cells. The graphical abstract illustrates key characteristics associated with cancers, such as the capacity to resist apoptosis [4], induce angiogenesis [5], replicate indefinitely [6-7], generate self-sufficient growth signals [8], disregard anti-growth signals [9], and invade tissues for metastasis [10-11]. These attributes empower cancer cells to achieve boundless growth, prolonged survival, and the ability to invade tissues. If left unchecked, these processes can lead to cancer cell expansion, invasion, and ultimately, the demise of the cancer patient.

The vast spectrum of bioactive compounds, abundantly present in various natural reservoirs, encompasses a diverse array of chemical entities with potent biological activities [12-13]. Among these sources, fruits, vegetables, and medicinal plants are particularly recognized for their rich content of bioactive compounds, offering a holistic and sustainable approach to cancer prevention [14-15]. The synergistic combination of these compounds, as found in whole foods, presents a unique advantage over isolated compounds, potentially

providing a comprehensive defense against the multifaceted aspects of cancer development [16].

The foundation of this exploration lies in the recognition that the traditional Western diet, often characterized by a deficiency in bioactive compounds, has been associated with an increased risk of cancer [17]. In contrast, populations adhering to diets rich in fruits and vegetables have demonstrated a reduced incidence of certain cancers [18]. This epidemiological evidence, coupled with advancements in molecular and cellular biology, has propelled the scientific community to delve into the mechanisms through which bioactive compounds exert their preventive effects.

Polyphenols, one class of bioactive compounds, have gained popularity for their antioxidant properties and their ability to modulate various signaling pathways implicated in cancer development [19]. Resveratrol, found in red grapes and wine, and EGCG (Epigallocatechin gallate), abundant in green tea, are examples of polyphenols that have shown promising anticancer effects in preclinical studies [20]. Their mechanisms of action include interference with cell cycle progression, induction of apoptosis, and inhibition of angiogenesis, collectively contributing to the prevention of cancer initiation and progression [19].

Alkaloids, another class of bioactive compounds predominantly sourced from medicinal plants, have a storied history in cancer treatment [21]. Vincristine and vinblastine, derived from the Madagascar periwinkle plant, have been integral components of chemotherapy regimens [22]. Recent research has shifted the focus towards exploring the preventive potential of alkaloids, investigating their role in impeding uncontrolled cell proliferation and metastasis [23].

Terpenoids, found in essential oils and plant extracts, have also emerged as noteworthy bioactive compounds with anticancer properties [24]. Their ability to modulate inflammatory pathways, inhibit angiogenesis, and induce apoptosis underscores their potential to prevent cancer growth [25]. Examples, such as artemisinin, derived from the sweet wormwood plant, have demonstrated promise in preclinical studies as potential agents for cancer prevention [26].

Various recent studies have focused on natural resources of bioactive compounds and tried to recognize their potential benefits [27-29]. The urgency to unravel the full potential of bioactive compounds in preventing cancer growth and progression is underscored by the increasing prevalence of cancer globally. This review aims to synthesize existing knowledge on the diverse classes of bioactive compounds, their mechanisms of action, and the cumulative evidence from preclinical studies. By doing so, we aim to provide a comprehensive understanding of the current landscape and pave the way for future research directions to ultimately contribute to the development of effective and accessible strategies for cancer prevention.

METHODS

Search strategy: To conduct a comprehensive review on the potential of bioactive compounds in preventing cancer growth and progression, a systematic approach was adopted to ensure inclusivity and reliability in the selection of relevant literature. Databases including PubMed, Web of Science, Scopus, FFHDJ (Functional Food Center/Food Science Publisher), and Google Scholar were queried. The search was conducted using a combination of keywords, MeSH (Medical Subject Headings) terms, and Boolean operators, such as "Bioactive compounds," "cancer growth," and relevant synonyms. The search strategy was tailored to the specific requirements of each database This systematic review has been registered in Inplasy. The registration details, including the review protocol, search strategy, and inclusion/exclusion criteria, are available upon request from the corresponding author. A PRISMA flowchart illustrating the search and selection process is presented in Figure 1.

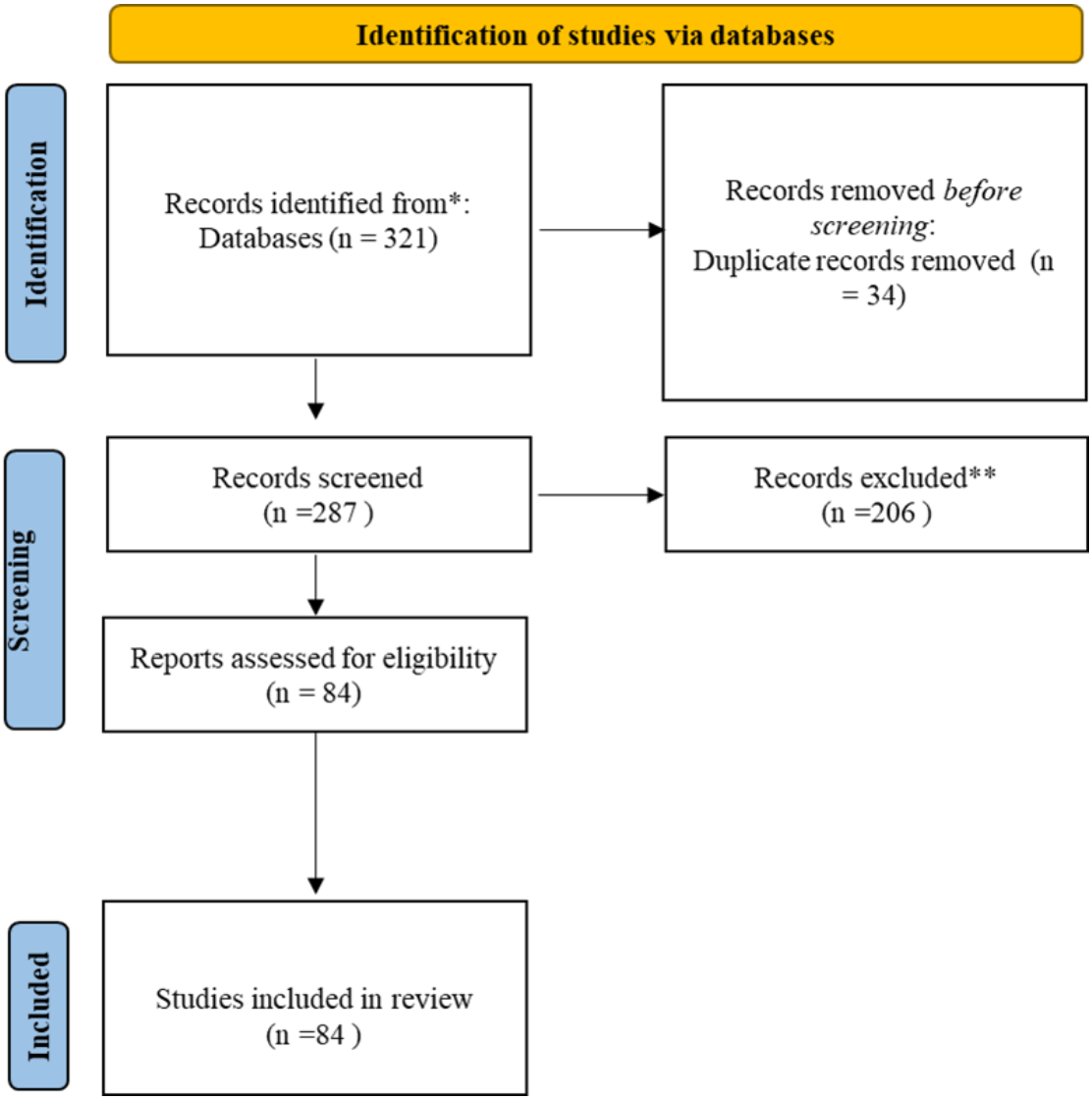


Figure 1. PRISMA flowchart.

Inclusion criteria: The inclusion criteria were established to ensure that selected articles were pertinent to the review objectives. These criteria encompassed peer-reviewed articles, clinical trials, systematic reviews, meta-analyses, and preclinical studies investigating the effects of bioactive compounds on cancer growth and progression.

Exclusion criteria: Articles that did not meet the predefined inclusion criteria were excluded from the review. Exclusion criteria included non-English articles, conference abstracts, editorial commentaries, letters to the editor, and studies lacking full-text availability.

Ethical considerations: Ethical considerations were considered throughout the study. This review does not involve any direct research on animals. Instead, it relies on the analysis of existing scientific literature. The ethical conduct of the original studies included in this review was assumed, and the authors of those studies are responsible for their adherence to ethical standards and animal welfare regulations.

Limitations: Time constraints and a focus on peer-reviewed articles may overlook relevant non-English sources, introduce database bias, and skew interpretations toward published literature. Despite

these, efforts were made to ensure integrity through rigorous search strategies and transparent reporting.

BIOACTIVE COMPOUNDS AND CANCER BIOLOGY

Polyphenols: Polyphenols, a diverse and widely found class of bioactive compounds, are emerging as formidable allies in the fight against cancer [30]. These compounds are abundantly present in an array of natural sources, including fruits, tea, and red wine, providing an accessible avenue for cancer prevention [31]. The multifaceted nature of polyphenols allows them to exert their anticancer properties through modulation of crucial cellular processes, such as the cell cycle, apoptosis, and angiogenesis, as shown in Figure 2 [30].

The anticancer potential of polyphenols lies in their ability to influence the machinery governing cell division. By modulating cell cycle checkpoints, polyphenols exert control over the pace and precision of cell division, inhibiting the unbridled proliferation characteristic of cancer cells [32]. This regulatory role in the cell cycle represents a fundamental aspect of polyphenol-mediated cancer prevention.

Apoptosis, or programmed cell death, is a pivotal mechanism through which polyphenols showcase their antineoplastic ability. Polyphenols have been observed to induce apoptosis in cancer cells, a process crucial for eliminating aberrant cells and preventing their uncontrolled growth [33]. The exploration of specific polyphenols and their unique pro-apoptotic mechanisms will be a focal point, and the impact of polyphenols on angiogenesis and the formation of new blood vessels, further contributes to their anticancer properties [34]. Polyphenols disrupt this process by inhibiting the formation of new blood vessels, thereby starving the tumors of their essential nutrients and oxygen. This intervention in the angiogenic cascade may encompass various pathway cascades [35].

The results of a study by Abbaszadeh and colleagues suggest that legume extracts, which are rich in polyphenols, could be combined with prooxidant drugs in cancer chemotherapy. This combination can potentially protect normal cells from the apoptosis-inducing effects of such drugs, while leaving malignant cells unaffected. Additionally, these extracts may provide protection against apoptosis-related disorders in non-malignant tissues and organs [36].

In the subsequent sections of this review, we will explore specific polyphenols, their diverse sources, and the mechanisms through which they manifest their anti-cancer effects. Each polyphenol, such as resveratrol found in the skin of red grapes and catechins abundant in green tea, brings a unique signature to preventing cancer growth and progression.

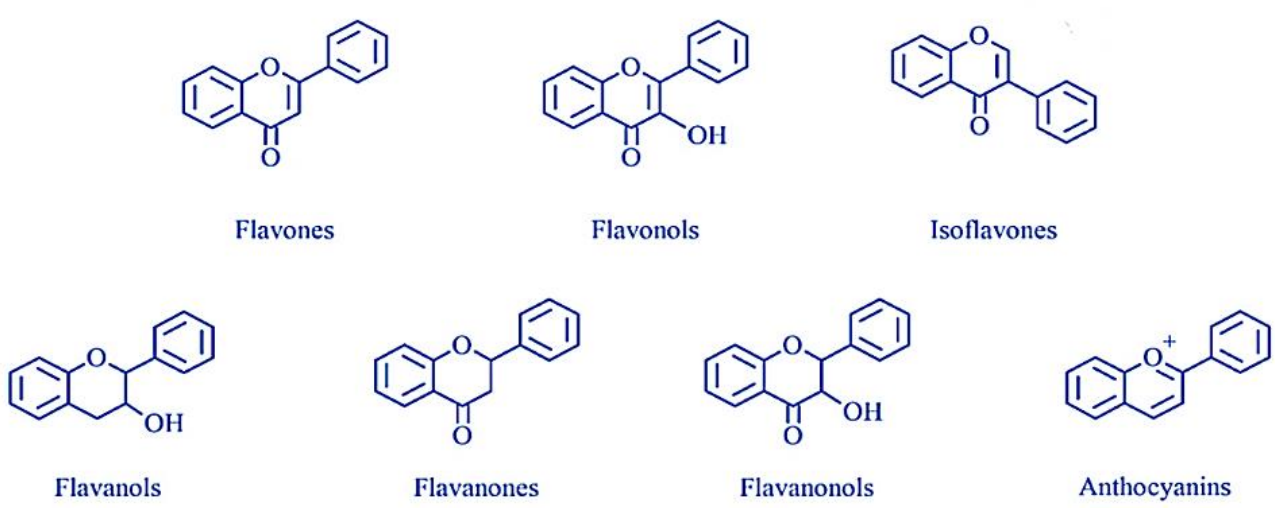


Figure 2. The fundamental arrangement of the primary subclasses of flavonoids varies [37].

Alkaloids: Alkaloids, a diverse class of naturally occurring compounds found in plants, have long been recognized for their therapeutic properties, particularly in cancer treatment, as shown in Figure 3 [38]. Two notable examples, vincristine and vinblastine, are instrumental components of chemotherapy regimens. However, recent scientific endeavors have extended to the preventive potential of alkaloids, by exploring how they hinder fundamental aspects of cancer development, including cell proliferation, metastasis, and angiogenesis.

At the forefront of alkaloid-mediated cancer prevention lies their ability to exert their influence at various stages of the cell cycle, leading to a disruption that curtails the division of cancer cells [39]. Moreover, metastasis, the spread of cancer cells to distant organs, stands as a challenge in cancer management [40]. By interfering with the molecular pathways involved in cell migration and invasion, alkaloids emerge as potential inhibitors against metastatic dissemination [41]. Finally, angiogenesis, the formation of new blood vessels, is a process crucial for sustaining the growth and progression of tumors [42]. Alkaloids can intervene with angiogenesis, disrupting the intricate signaling pathways that support the development of new vascular networks [43].

As we explore the role of alkaloids in cancer prevention, our aim is to examine their historical significance in cancer treatment and understand their potential to hinder the inception and progression of cancer. Alkaloids emerge as a promising frontier for effective strategies to prevent the growth and spread of cancer.

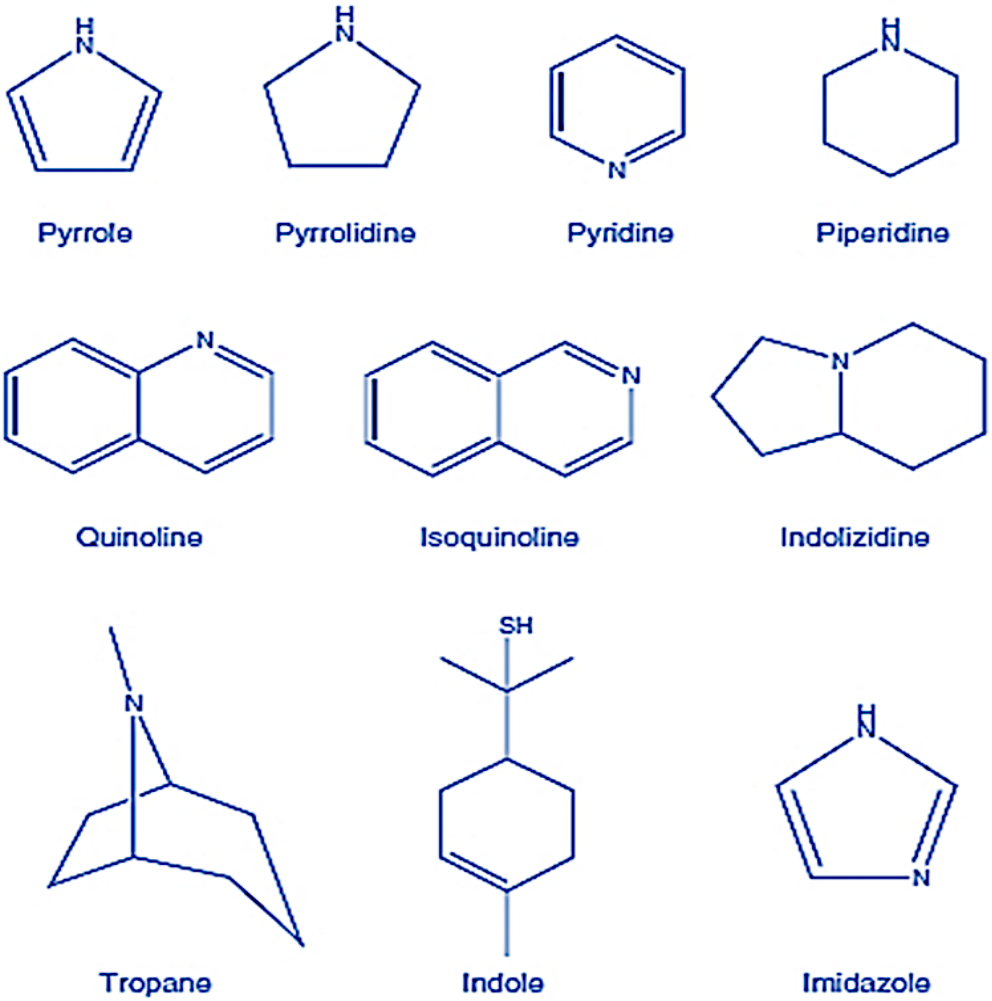


Figure 3. The fundamental arrangement of the primary subclasses of alkaloids varies [44].

Terpenoids: Terpenoids, a diverse class of compounds abundantly found in essential oils and various plant extracts, carry therapeutic potential in the realm of cancer prevention, as shown in Figure 4 [45]. Renowned for their anti-inflammatory and anti-cancer activities, terpenoids emerge as versatile players in the intricate dance between nature and malignancy [46]. This comprehensive review endeavors to cast a spotlight on the specific terpenoids, their natural sources, and the orchestrated roles they play in thwarting the relentless progression of cancer.

Terpenoids exhibit various biological activities, with anti-inflammatory and anti-cancer effects standing out prominently. The journey into the world of terpenoids begins by unraveling their anti-inflammatory abilities, which not only addresses chronic inflammation as a cancer promoting factor, but also sets the stage for a cascade of anti-cancer mechanisms [45]. This review will precisely navigate through the complex pathways that terpenoids utilize to alleviate inflammation, thus laying the groundwork for their broader cancer-preventive effects. Terpenoids' anti-cancer activities extend beyond inflammation, encompassing countless molecular pathways that collectively impede cancer progression [25].

Understanding the natural sources of terpenoids is imperative for understanding their potential applications in cancer prevention. Whether derived from the resin of trees, the rinds of citrus fruits, or the leaves of medicinal plants, terpenoids encapsulate the diverse essence of nature's pharmacopeia [47]. As this review unfolds, it aims to not only provide a comprehensive catalog of specific terpenoids, but also to illuminate the collective impact of these compounds in preventing cancer progression. Terpenoids, with their botanical origins and complex molecular structure, stand poised as nature's profound contribution to the ongoing quest for effective strategies in cancer prevention.

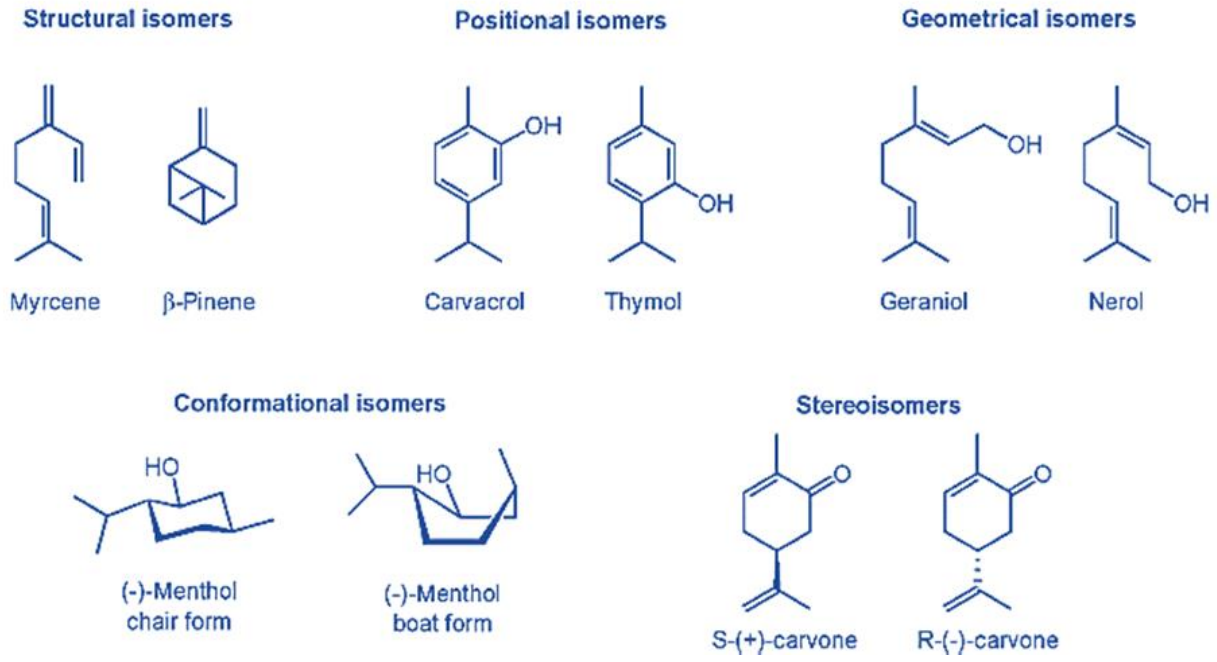


Figure 4. Primary types of isomerism observed in terpenoids.

MECHANISM OF ACTION

Cell cycle regulation: The cell cycle, an accurately orchestrated series of events governing cell division, stands as a cornerstone in maintaining cellular integrity. Bioactive compounds, sourced from diverse natural origins, navigate the cell cycle checkpoints, strategically

intervening to uphold the harmony and balance of cellular replication [48]. This comprehensive review dissects the nuanced interactions between bioactive compounds and key cell cycle regulators.

As guardians of genomic stability, bioactive compounds intricately influence the G1, S, and G2 phases of the cell cycle, ensuring that each transition is controlled and monitored [49]. The review outlines the specific bioactive compounds known for their prowess in halting cell cycle progression, emphasizing their diverse sources and mechanisms of action. Whether derived from fruits, vegetables, or medicinal plants, these compounds examine the reliability of DNA replication and protection against the aberrant proliferation that characterizes cancer cells [50].

Moreover, the review explores the broader implications of bioactive compound-mediated cell cycle modulation in preventing uncontrolled cell division. By disrupting the cycle at critical junctures, these compounds impede the unchecked proliferation of cancer cells, inducing a state of cellular quiescence or in some cases, triggering programmed cell death [51]. Understanding the specific points of intervention and the diverse pathways through which bioactive compounds influence the cell cycle checkpoints is pivotal for unraveling their preventive effects against uncontrolled cell division, marking a promising avenue in the ongoing quest for effective strategies in cancer prevention [52].

Apoptosis induction: Gaining a comprehensive understanding of the complex mechanisms involved in cancer prevention is essential for advancing therapeutic strategies. Notably, inducing apoptosis in cancer cells stands out as a crucial and multifaceted mechanism utilized by bioactive compounds. Apoptosis, or programmed cell death, stands as a defense mechanism against the aberrant growth of cancer cells [53]. This section delves into the diverse array of apoptotic pathways that bioactive compounds navigate to exert their anti-cancer effects. Bioactive compounds influence apoptotic pathways. The intrinsic pathway, regulated by mitochondria, involves the release of proapoptotic factors that initiate cell death. In contrast, the extrinsic pathway is triggered by external signals that bind to death receptors on the cell surface, setting off a cascade of events that lead to apoptosis. Bioactive compounds have been shown to modulate both these pathways, highlighting their versatile nature in combating cancer [52, 54]. Polyphenols, for instance, demonstrate their apoptotic abilities by modulating Bcl-2 family proteins, disrupting mitochondrial integrity, and activating caspase cascades [55]. Alkaloids, on the other hand, exhibit various apoptotic inductions, impacting the delicate balance between pro-apoptotic and anti-apoptotic signals within cancer cells [56]. Moreover, terpenoids exert their effects through multiple mechanisms, including interference with cell cycle progression, induction of oxidative stress, and the modulation of signaling pathways associated with apoptosis [57, 58].

Studies have indicated that certain terpenoids can disrupt the cell cycle by arresting cells at specific phases, such as the G1 or G2/M phases, leading to impaired proliferation and promoting apoptotic responses [59]. Additionally, terpenoids have been demonstrated to increase oxidative stress in cancer cells, producing reactive oxygen species (ROS) that cause DNA damage and subsequently induce apoptosis [60].

Furthermore, the ability of terpenoids to interact with key signaling pathways involved in apoptosis provides another layer of their anticancer potential. These compounds can influence various cellular pathways, such as the PI3K/AKT and MAPK pathways, thereby promoting a shift in the balance towards pro-apoptotic signals [61].

The complex interaction between polyphenols, alkaloids, and terpenoids highlights the extensive array of natural compounds that can induce apoptosis in cancer cells. Leveraging the synergistic effects of these diverse bioactive molecules offers potential for developing

innovative therapeutic strategies against cancer. Further investigation into the specific mechanisms and possible combinatorial approaches involving these natural compounds is essential for a deeper understanding and more effective application in cancer treatment.

Anti-angiogenic properties: Angiogenesis, the process of forming new blood vessels, represents a critical hallmark in the progression of cancer [62]. This phenomenon plays a crucial role in sustaining malignant tissues by facilitating the supply of essential nutrients and oxygen [63]. In the pursuit of effective cancer treatments, bioactive compounds have emerged as promising agents capable of disrupting this critical angiogenic process.

A primary target of these bioactive compounds is the vascular endothelial growth factor (VEGF) pathway. Through the modulation of signaling pathways such as VEGF, these compounds effectively inhibit the formation of new blood vessels, a process crucial for the sustained development of tumors. This inhibition bears profound implications for cancer prevention, as it directly impedes the tumor's ability to thrive and metastasize [64]. As an example, in a study by Zhiping and colleagues [65], polyphenols, specifically gallic acid, exhibited significant anti-cancer properties in two ovarian cancer cell lines (OVCAR-3 and A2780/CP70). Gallic acid, in conjunction with baicalein, tangeretin, nobiletin, and baicalin, demonstrated substantial inhibition of VEGF secretion, comparable to the effects of cisplatin, a conventional chemotherapy agent. These results imply that gallic acid possesses the potential to hinder cell proliferation and may be regarded as a promising agent for the treatment of ovarian cancer [65].

The potential of bioactive compounds in suppressing angiogenesis opens new paths for therapeutic strategies, offering a nuanced and targeted approach to impede cancer progression. This emerging field not only underscores the complexity of molecular interactions within the human body, but also highlights the transformative impact that bioactive compounds can have in reshaping the landscape of cancer treatment and prevention. As research continues to unveil the intricacies of angiogenesis, harnessing the power of bioactive compounds holds great promise in the ongoing battle against cancer.

PRECLINICAL EVIDENCE

In vitro studies: This section provides a comprehensive overview of findings derived from in vitro studies aimed at elucidating the nuanced impact of bioactive compounds on various cancer cell lines. In vitro investigations serve as a critical foundation for understanding the intricate interactions between these compounds and cancerous cells, shedding light on dose-dependent effects and potential synergistic actions when different compounds are combined.

In examining the dose-dependent effects, researchers have meticulously explored the concentration response relationships of bioactive compounds. This approach not only delves into the therapeutic efficacy of these compounds, but also unveils potential thresholds beyond which adverse effects may prevail. The dose response dynamics offer valuable insights into the fine balance required for optimal anticancer effects while minimizing any detrimental impact on normal cellular functions [66]. Moreover, the exploration of potential synergies between different bioactive compounds has emerged as a focal point in contemporary research. Combinatorial approaches, where various compounds are concurrently administered, have shown promising outcomes in amplifying their individual anticancer effects. The synergistic interactions may involve the potentiation of apoptosis induction, cell cycle arrest, or inhibition of metastatic pathways. Understanding these synergies is essential for optimizing therapeutic regimens and developing tailored interventions that harness the collective power of bioactive compounds [67].

Several studies have explored the molecular mechanisms underlying the observed effects, unraveling the intricate signaling pathways and cellular processes modulated by bioactive compounds. This mechanistic insight not only enhances our understanding of cancer biology but also paves the way for the rational design of targeted therapies [68].

In a study, administering EGCG—a polyphenol predominantly found in green tea—to androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells led to a dose-dependent reduction in cell proliferation and an elevation in apoptosis, as demonstrated by ELISA assays and the detection of DNA fragmentation [69]. These effects can be attributed to EGCG's capacity to inhibit COX-2 expression, which is pathologically elevated in conditions like tumor growth and angiogenesis [70].

A study evaluated the antineoplastic effects of kaempferol-Zn compared to free kaempferol on the human esophageal cancer cell line EC9706. MTT assay results showed that kaempferol-Zn had double the cytotoxic potency of free kaempferol. Atomic force microscopy (AFM) revealed morphological and ultrastructural alterations in the cellular membrane induced by kaempferol-Zn at the subcellular or nanometer scale. Furthermore, flow cytometric analysis demonstrated that kaempferol-Zn triggered apoptosis in EC9706 cells by modulating intracellular calcium ions [71].

Kaempferol was also found to inhibit the proliferation of human colon cancer cells HCT116 and DLD1 in a dose-dependent manner. Moreover, kaempferol treatment delayed the G1 phase of the cell cycle and induced apoptosis. Considering that aerobic glycolysis is a major energy source for many tumor types, including colon cancer, it is significant that kaempferol treatment disrupted glucose consumption, leading to decreased lactic acid accumulation and ATP production [72]. In another study, kaempferol exhibited strong antiproliferative and anti-migratory effects in human bladder cancer EJ cells. Kaempferol induced apoptosis in a dose-dependent manner, as evidenced by increased caspase-3 cleavage. This apoptotic effect was linked to the modulation of the PTEN/PI3K/Akt pathway, with kaempferol significantly enhancing PTEN expression and reducing Akt phosphorylation. The apoptotic impact of kaempferol was partially attenuated in PTEN-knockdown cells [73]. The anticancer effects of kaempferol were attributed to its inhibition of EGFR-related Src, ERK1/2, and AKT pathways. These findings suggest that kaempferol, recognized for its anti-viability and antioxidant properties, can act as a safe anti-migration agent in human pancreatic cancer cells [74].

A research study revealed that treating A549 cells with TGF-β1 and resveratrol inhibits the initiation of TGF-β1-induced epithelial-mesenchymal transition (EMT). Specifically, at a concentration of 20 μM, resveratrol enhances the expression of the epithelial marker E-cadherin, while suppressing the mesenchymal markers fibronectin and vimentin during EMT initiation. Additionally, resveratrol inhibits the expression of EMT-inducing transcription factors Snail1 and Slug. Furthermore, it prevents the TGF-β1-induced increase in cell adhesion, migration, and invasion in A549 lung cancer cells [75]. As previously mentioned, one of the sources of polyphenols is wine. A study demonstrated that red wine inhibited cell proliferation and reduced clonogenic survival in A549 cells, even at low concentrations (0.02%). Notably, red wine significantly decreased both basal and EGF-stimulated Akt and Erk phosphorylation while increasing levels of total and phosphorylated p53 (Ser15). Control experiments confirmed that the anti-proliferative effects of wine were independent of its ethanol or resveratrol content and were not influenced by glucose transport into cancer cells. Additionally, white wine also inhibited clonogenic survival, although at higher doses (0.5-2%), and reduced Akt phosphorylation. These effects

on Akt phosphorylation were similarly observed in H1299 cells for both red and white wine [76].

A study evaluated the amount of Alkaloids contained in P.Harmala L. seeds, using HPTLC, and the subsequent in vitro results showed the extracts of these seeds inhibit human DNA topoisomerase I, and based on the HPTLC results, this effect was explained as the effect of the seed's alkaloid content [77]. An additional in vitro research study focused on alkaloids extracted from Nelumbo nucifera Gaertn. cv. Rosa-plena, commonly known as lotus, an aquatic crop indigenous to Asia and Africa. The study revealed that 7-hydroxydehydronuciferine, one of the fifteen compounds extracted, markedly suppressed the proliferation of prostate, melanoma, and gastric cancer cells [78]. Berberine is an Alkaloid compound that can be extracted from the stems and roots of various plants, such as *Berberis aristate*, an Indian medicinal plant that is used for its anti-microbial, anti-hepatotoxic, anti-cancer, and anti-oxidant effects [79]. This compound, exhibits antineoplastic activities through its ability to induce cell apoptosis (via many pathways) and to reduce cell proliferation, especially in breast cancer cells [80]. Using Vincristine (which is an antitumor agent widely used) with a dose that does not cause cell toxicity, in combination with Berberine on hepatocarcinoma cells, resulted in increased cell apoptosis induction and growth inhibition, which means that the adverse effects of Vincristine can be avoided in hepatocarcinoma therapy [81]. A 2015 research study concluded that Berberine had anticancer effects on head and neck carcinoma cells. According to the study, berberine increased the apoptosis rate in FaDu cells, including many pathways such as those mitochondria-dependent as well as the upregulation of apoptotic ligands. Furthermore, cells treated with berberine, showed reduced migration in addition to increased expression of the tumor suppressor p53, after 24 hours [82]. Another study concerning apoptosis of human tumor cells, exhibited that Evodiamine increased apoptosis in cancer cells mainly by activating caspase-dependent apoptotic pathways [83]. In a structural-based screening study, Evodiamine was found to have human topoisomerase I inhibitory effects in vitro, after introducing various groups to its indole nitrogen atom. Substitution of benzoyl groups had the best effectiveness for antitumoral activities and spectrum [84]. Another study's findings revealed that in vitro, evodiamine decreased the metastatic potential and invasion of MDA-MB-231 human breast cancer cells. These effects were associated with the downregulation of MMP-9, urokinase-type plasminogen activator (uPA), and uPAR expression. Additionally, apoptosis was induced in tumor cells, primarily through a combination of extracellular signal-regulated kinase inhibitor PD98059 or the p38 mitogen-activated protein kinase (p38 MAPK) inhibitor SB203580 [85]. Cytotoxic abilities of Magnoflorine and Lanuginosine were evaluated on hepatocellular carcinoma and brain tumor cell lines, with the first proving more effective than the latter. It was also concluded that these two compounds did not have significant inhibitory effects on the cervix tumor cell line [86]. Hirsutine, an alkaloid found in plants of the Uncaria genus, not only demonstrated antimetastatic activity by targeting NF-κB activation in murine breast cancer, but also exhibited significant cytotoxicity against HER2-positive/p53-mutated breast cancer cell lines, such as MDA-MB-453 and BT474. Moreover, this compound induced caspase-related apoptotic cell death and DNA damage by upregulating γH2AX expression. It suppressed HER2, NF-κB, and Akt pathways, while activating the p38 MAPK pathway in MDA-MB-453 cells [87, 88].

In a study on terpenoids, elemene exhibited dose- and time-dependent inhibitory effects on the growth of HEp-2 cells, with an IC50 of 346.5 µM after 24 hours of incubation. Additionally, apoptosis was heightened in cells treated with elemene. The study suggests that elemene may enhance caspase-3 activity, leading to the inhibition of protein expression of eIFs (4E, 4G), bFGF, and

VEGF [89]. Another research study investigated the impact of β-elemene on cell growth in non-small cell lung cancer (NSCLC) cell lines compared to normal lung fibroblast and bronchial epithelial cell lines. The findings suggest that β-elemene effectively inhibits the growth of NSCLC cells while exerting minimal effects on normal lung cells. The compound induced cell cycle arrest at the G2-M phase in NSCLC cells, accompanied by specific alterations in the levels of various proteins involved in cell cycle regulation. These alterations included decreased levels of cyclin B1 and phospho-Cdc2 (Thr-161), along with increased levels of p27kip1 and phospho-Cdc2 (Tyr-15). Furthermore, β-elemene reduced the expression of Cdc25C, which activates Cdc2, while enhancing the expression of Chk2, which inactivates Cdc25C. Additionally, β-elemene induced apoptosis in NSCLC cells by activating caspase-3, -7, and -9, decreasing the expression of the anti-apoptotic protein Bcl-2, promoting the release of cytochrome-C from mitochondria, and increasing levels of cleaved caspase-9 and poly(ADP-ribose) polymerase [90]. In another study, the antiproliferative effects of β-elemene were assessed on androgen-insensitive prostate carcinoma cells DU145 and PC-3, as well as on various other cancer cell lines derived from the brain, breast, cervical, colon, and lung. The study revealed that the impact of β-elemene on cancer cells is dose-dependent, with half-maximal inhibitory concentration (IC50) values ranging from 47 to 95 µg/ml (230–465 µM). Moreover, apoptosis was induced in prostate cancer cells in a dose- and time-dependent manner, as evidenced by TUNEL assay and flow cytometric analysis using annexin V/propidium iodide staining. This apoptotic effect was associated with decreased levels of the anti-apoptotic protein Bcl-2, increased release of cytochrome c, and activation of poly (ADP-ribose) polymerase (PARP) and caspases-3, -7, -9, and -10 [91].

An investigation explored the potential antineoplastic properties of thymol on HL-60 cells, a type of acute promyelocytic leukemia. The research revealed that thymol exhibited dose-dependent cytotoxic effects on HL-60 cells within a 24-hour period, while demonstrating no cytotoxicity in normal human peripheral blood mononuclear cells (PBMCs). The observed cytotoxic impact of thymol on HL-60 cells appears to be associated with its ability to arrest the cell cycle at the sub G0/G1 phase and induce apoptotic cell death, evidenced by the fragmentation pattern of genomic DNA. Moreover, thymol triggered a significant increase in reactive oxygen species (ROS) production, an elevation in mitochondrial H2O2 generation, and a decrease in mitochondrial membrane potential. Western blot analysis revealed a dose-dependent increase in Bax protein levels alongside a simultaneous reduction in Bcl2 protein expression upon exposure to thymol. Additionally, it demonstrated the activation of caspase-9, -8, and -3, along with concurrent PARP cleavage, indicative of caspase-dependent apoptosis. Furthermore, the impact of thymol on apoptosis-inducing factor (AIF) was investigated to exclude the involvement of alternative mechanisms in apoptosis induction. Thymol prompted the translocation of AIF from mitochondria to the cytosol and nucleus, indicating its capacity to induce caspase-independent apoptosis [92]. Another research study proposed that thymol and carvacrol may contribute to the regulation of T cell activity by reducing the production of interleukin-2 (IL-2) and interferon-gamma (IFN-γ), possibly through the downregulation of AP-1 and NFAT-2 transcription factors. This suggests their potential usefulness in mitigating T cell hyperactivity linked with immune-mediated diseases [93]. The influence of menthol on the gene expression profile of PC-3 prostate cancer cells was investigated using DNA microarray analyses. Gene set enrichment analysis indicated that menthol primarily affects the expression of genes related to the cell cycle. Experimental evidence further confirmed that menthol induces G2/M arrest in these cells. Notably, it decreased the expression of polo-like

kinase 1 (PLK1), a key regulator of G2/M phase progression, and inhibited its downstream signaling pathways [94]. Auraptene, a monoterpenoid, has been the subject of investigation in various studies. For example, one study presented novel evidence illustrating that auraptene effectively reduces the characteristics of esophageal stem-like cancer cells. This was accomplished by enhancing sensitivity to chemical agents and reducing the expression of CD44 and BMI-1 markers [95].

The findings of one study revealed that carvacrol, another terpenoid, displayed cytotoxic effects against MCF-7 cancer cells in a dose-dependent manner at both 24 and 48-hour intervals ($p < 0.05$). Treatment with carvacrol induced apoptosis in MCF-7 cells through activation of the p53-dependent and Bcl-2/Bax pathways. Furthermore, carvacrol treatment upregulated the expression of caspase-3, -9, and -6 genes, leading to genomic DNA fragmentation. In another study, the essential oil extracted from Tunisian Nigella sativa seeds, along with its primary terpenes including p-cymene, γ-terpinene, thymoquinone, β-pinene, carvacrol, terpinen-4-ol, and longifolene, exhibited significant inhibitory effects on the growth of A-549 and DLD-1 cancer cell lines [97].

In another study, the application of various concentrations of N. sativa oil (except for 100 µg/mL for 48 hours) did not affect the number of tested glioma (T98G), prostate (LnCaP), and mouse embryonic fibroblast cell lines. However, treatment with thymoquinone significantly reduced the number of all cells. Furthermore, thymoquinone induced apoptosis by activating caspase-9. Additionally, the results of yet another study on thymoquinone indicated that the compound inhibited the metastasis of renal cell carcinoma (RCC) cells by inducing autophagy through the AMPK/mTOR (AMP-activated Protein Kinase/Mammalian target of rapamycin) signaling pathway, (Table1) [99].

In vivo studies: The exploration of bioactive compounds in the context of cancer extends beyond in vitro studies to encompass preclinical investigations utilizing animal models, a pivotal phase that bridges the gap between cellular responses and the complex in vivo environment. This section delves into the wealth of knowledge garnered from these preclinical studies, accentuating crucial aspects such as bioavailability, toxicity profiles, and optimal dosages, all of which are paramount in translating laboratory findings into potential therapeutic applications.

Bioavailability, a key determinant of a compound's efficacy, represents the fraction of an administered dose that reaches systemic circulation and is available to exert its biological effects [100]. In preclinical studies, researchers meticulously assess the bioavailability of bioactive compounds to ascertain their capacity to reach target tissues at concentrations conducive to exerting anticancer effects. This consideration is vital for understanding the pharmacokinetic profile of these compounds, influencing decisions regarding dosage regimens and administration routes for subsequent clinical applications. As for bioavailability of polyphenols, recent studies have pointed out the importance of considering matrix effect, interactions between GI enzymes and also other ingested food, genetics, gender and age, while talking about the positive health properties of polyphenols [101].

Toxicity profiles constitute another critical facet of preclinical investigations. Rigorous evaluation of the safety profile of bioactive compounds in animal models is indispensable for gauging potential adverse effects and establishing a therapeutic window. Researchers meticulously assess systemic toxicity, organ-specific effects, and any signs of cumulative toxicity over prolonged exposure. Understanding the toxicological implications guides the refinement of dosage regimens to ensure therapeutic benefits while minimizing the risk of harm.

Optimal dosages, a pivotal parameter in the translation of preclinical findings to clinical applications,

are meticulously determined through systematic experimentation. Researchers explore a range of doses to identify the threshold at which maximum therapeutic efficacy is achieved without undue toxicity. This dosage optimization process considers factors such as compound half-life, distribution within tissues, and the dynamic interplay between the compound and the host organism.

Indeed, focusing on the anticarcinogenic effects of polyphenols, numerous studies have assessed the impact of these compounds on cancerous cells. For example, a study conducted back in 1997 concluded that resveratrol, commonly found in various food products such as grapes, inhibited cyclooxygenase, demonstrating its anti-inflammatory effects. Additionally, it induced differentiation in human promyelocytic leukemia cells. Intriguingly, resveratrol also inhibited the development of preneoplastic lesions in carcinogen-treated mouse mammary glands in culture and suppressed tumorigenesis in a mouse skin cancer model [102]. In an in vivo study in nude mice, 4'-chloro-3,5-dihydroxystilbene, a resveratrol derivative, demonstrated potential antineoplastic activity by hindering tumor growth in lung adenocarcinoma A549 cells. This suggests that the observed cellular responses may contribute to its antitumor effects, possibly by inducing cell death pathways and impairing cellular homeostasis within cancer cells [103].

Some derivatives of Evodiamine, an alkaloid compound, were found to have a good antitumor effect via in vivo studies, alongside an acceptable toxicity profile which makes it an ideal candidate for further investigation around cancer treatment [104]. Moreover, the administration of 10 mg per kg Evodiamine was proven to be effective in reducing tumor growth and pulmonary metastasis in breast cancer patients [85]. Duocarmycin, is an alkaloid produced by *Streptomyces* sp. Bacterium. A new hydrolysable prodrug of duocarmycin and CC-1065 family, a heterocyclic carbamate prodrug of seco-CBI-indole$_2$, was tested in vivo and the results showed that compared to the parent drug, this compound had a greater efficacy, bigger therapeutic window, and a more convenient releasing method which made it possible to use doses of 150-fold higher than the parent drug [105]. Pre-treatment of colon 26-L5 carcinoma cells and Lewis lung carcinoma cells with evodiamine led to a markedly reduced rate of lung and liver metastasis in mice inoculated with these cells. The results also indicated that among similarly structured compounds evaluated simultaneously, the anti-metastatic and inhibitory effects of evodiamine are likely attributed to the presence of a methyl group at N-14 and the configuration of hydrogen at C-13b [106]. Evidence suggests inhibitory effects of berberine at a dose of 50 mg per kg per day in a human colorectal adenocarcinoma xenograft in nude mice. Moreover, there was apparent synergism between berberine and fluorouracil (5-FU), indicating the potential usefulness of this compound in colorectal adenocarcinoma therapy [107].

Terpenoids have been the subject of numerous studies exploring their anticancer characteristics. According to one study, intraperitoneal administration of elemene stalled the growth of tumors derived from HEp-2 cells transplanted into nude mice. Additionally, compared to control groups, elemene significantly suppressed the protein expression of certain factors, namely eukaryotic initiation factors (eIFs) 4E and 4G, basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF). Moreover, a decrease in microvessel density (MVD) was observed, indicating a reduction in blood vessel formation within the tumors. These findings suggest that elemene may possess anti-tumor properties, potentially through inhibiting factors involved in tumor growth and angiogenesis [89]. In a study using a xenograft tumor model of oral squamous cell carcinoma (OSCC) in nude mice, animals were administered cisplatin, β-elemene, or a combination of both. The effects of these treatments were evaluated by measuring the volume and weight of the transplanted

tumors. Additionally, the levels of phosphorylated JAK2 (p-JAK2) and phosphorylated STAT3 (p-STAT3) expressions were assessed, along with the degree of apoptosis in the xenograft tumor tissues. The results suggested that the combination of β-elemene and cisplatin may represent a promising therapeutic strategy for oral squamous cell carcinoma by synergistically suppressing tumor growth, inducing apoptosis, and targeting the JAK2/STAT3 signaling pathway [108]. β-elemene was evaluated in vivo using nude mice, which lack a fully functional immune system. In another experiment, it was found to inhibit tumor growth or reduce tumor size, suggesting potential antineoplastic properties. Furthermore, apoptosis was induced, and autophagy was observed within the tumor cells. These effects hold promise in the context of cancer treatment, as inhibiting tumor growth and inducing cell death are essential goals in cancer therapy [109]. A study revealed notable antitumor effects of thymol in Cal27-derived tumors, with further confirmation of its anticancer properties in HeLa-derived xenografts, suggesting efficacy across different tumor types. Calcium imaging demonstrated calcium influx in Cal27 cells, which was reversed by the TRPA1 antagonist, HC030031. However, no calcium influx was observed in HeLa cells, indicating that TRP channels do not regulate thymol's cytotoxicity. This finding was supported by cell viability assays, showing that pre-treatment with HC030031 did not affect thymol's cytotoxicity. Instead, studies on mitochondrial transmembrane potential revealed that thymol induces significant depolarization and apoptosis, highlighting an alternative mechanism of action [110]. D-limonene demonstrated inhibitory effects on the growth of lung cancer cells and suppressed the growth of transplanted tumors in nude mice. Treatment with D-limonene increased the expression of apoptosis and autophagy-related genes in tumors. Additionally, the use of chloroquine, an autophagy inhibitor, and knockdown of the atg5 gene suppressed the apoptosis induced by D-limonene (Table1) [111].

Table 1. Effects of bioactive compounds on cancer cells: summary of in vitro and in vivo studies.

Bioactive Compound	Cancer Type	Effect on Cancer Cells	Reference
EGCG	Prostate carcinoma	Decreased cell growth, increased apoptosis	[69]
Kaempferol	Esophageal cancer	Cytotoxic, induced apoptosis, regulated calcium ions	[71]
Kaempferol	Colon cancer	Inhibited proliferation, delayed cell cycle, induced apoptosis, impaired glucose consumption	[72]
Kaempferol	Bladder cancer	Induced apoptosis, modulated PTEN/PI3K/Akt pathway	[73]
Kaempferol	Pancreatic cancer	Inhibited EGFR-related pathways, anti-migratory	[74]
Resveratrol	Lung cancer	Inhibited epithelial-mesenchymal transition, reduced cell adhesion, migration, and invasion	[75]
Red Wine	Lung cancer	Inhibitory effects on cell proliferation, reduced phosphorylation of Akt and Erk	[76]

Bioactive Compound	Cancer Type	Effect on Cancer Cells	Reference
Berberine	Breast cancer	Induced cell apoptosis, reduced cell proliferation	[80]
Evodiamine	Various cancer types	Increased apoptosis, inhibited metastasis, induced autophagy	[83-85, 106]
Magnoflorine and Lanuginosine	Hepatocellular carcinoma, Brain tumor	Varying efficacy, no significant inhibition on cervix tumor cell line	[86]
Hirsutine	Breast cancer	Cytotoxic, antimetastatic, induced caspase-related apoptotic cell death	[87-88]
Elemene	Various cancer types	Inhibited cell growth, induced apoptosis, inhibited angiogenesis	[89]
Thymol	Acute promyelotic leukemia	Cytotoxic, induced apoptosis, altered mitochondrial function	[92]
Menthol	Prostate cancer	Altered gene expression related to cell cycle regulation, induced G2/M arrest	[94]
Auraptene	Esophageal cancer	Diminished characteristics of cancer stem cells	[95]
Carvacrol	Breast cancer	Cytotoxic, induced apoptosis through p53/Bcl-2/Bax pathways	[96]
Thymoquinone	Glioma, Prostate cancer	Varying effects, induced apoptosis, inhibited metastasis	[98-99]
D-limonene	Lung cancer	Inhibited cell growth, induced apoptosis and autophagy	[111]

CONCLUSION

In summary, the investigation into the impact of bioactive compounds on cancer has revealed significant potential in both the prevention and treatment of this pervasive disease. Derived from various natural plant sources, these compounds offer a promising avenue for protection against cancer and as potential treatment approaches. Numerous studies have demonstrated their ability to inhibit tumor growth, induce apoptosis, and mitigate the risk of metastasis. Furthermore, bioactive compounds have shown promise in enhancing the efficacy of conventional cancer therapies, serving as valuable adjuvant treatments. However, further research is needed to fully understand the underlying molecular mechanisms and establish optimal dosages for clinical applications. The ongoing exploration of bioactive compounds holds great promise for the development of novel and effective strategies in the ongoing fight against cancer. Looking ahead, future research efforts should prioritize unraveling the precise molecular mechanisms underlying the effects of bioactive compounds on cancer. Furthermore, establishing optimal dosages and exploring their synergistic interactions with existing cancer treatments are crucial steps toward translating these findings into clinical applications. By addressing these key areas, we can further enhance our understanding and utilization of bioactive compounds in the ongoing battle against cancer. The impact of this research lies in its contribution to the ongoing battle against cancer, a leading cause of global mortality. With cancer-related deaths on the rise in recent years, there is an urgent need for effective interventions. This research highlights the potential of bioactive compounds derived from natural plants as potent agents in combating cancer. By focusing on polyphenols, alkaloids, and terpenoids, the study consolidates evidence from preclinical studies to

elucidate their anticancer effects. Furthermore, it delves into the molecular mechanisms through which these compounds exert their therapeutic properties, drawing insights from cell and animal-based research. Overall, this comprehensive review sheds light on promising avenues for the development of novel cancer therapies and strategies to enhance chemotherapy outcomes while minimizing adverse effects.

The novelty of this work: The novelty of our review lies in its synthesis of the latest research findings, offering a comprehensive overview of the diverse bioactive compounds and their multifaceted roles in cancer prevention and treatment. By shedding light on this promising area of study, we pave the way for the development of novel and effective strategies in the ongoing battle against cancer.

Bioactive compounds in future cancer therapy: The data on the anticancer effects of polyphenols, alkaloids, and terpenoids hold significant potential for future cancer research and treatment strategies. These insights can aid in developing new therapeutic agents, designing effective combination therapies, and advancing personalized medicine. The compounds' potential in overcoming drug resistance and reducing adverse effects can enhance patient outcomes. Additionally, the data can inform preventive strategies and dietary recommendations, contribute to clinical trials, and drive further mechanistic studies. Overall, leveraging these natural bioactive compounds could lead to innovative, effective cancer treatments and improved global health outcomes.

Correlation of bioactive compounds with functional foods research: The data on the anticancer effects of polyphenols, alkaloids, and terpenoids strongly align with the research focus of Functional Foods in Health and Disease (FFHD). Both emphasize the role of biologically active compounds in promoting health and managing disease. Insights from the review can inform the development of functional foods aimed at cancer prevention and management, supporting the goals of Functional Food Science. This interdisciplinary approach highlights the potential for new dietary strategies to enhance cancer treatment and overall wellness.

Data availability statement: The data that support the findings of this study are available from the corresponding author on request.

List of Abbreviations: EGCG, Epigallocatechin Gallate; FFHDJ, Functional Food Center/Food Science Publisher; MeSH, Medical Subject Headings; ROS, Reactive Oxygen Species; VEGF, Vascular Endothelial Growth Factor; EIFs, Eukaryotic Initiation Factors; BFGF, Basic Fibroblast Growth Factor; MVD, Microvessel Density; OSCC, Squamous Cell Carcinoma; p-JAK, Phosphorylated JAK2; p-STAT3, Phosphorylated STAT3.

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