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Review

Dietary Polyphenols Intake and the Risk and Treatment of Colorectal Cancer

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ABSTRACT

Backgrounds: Colorectal cancer (CRC) is a significant global health concern, accounting for nearly 700,000 deaths each year, with risk factors. Including genetic mutations and lifestyle choices. Recent studies suggest dietary polyphenols, naturally occurring compounds in plant-based foods, may offer protective benefits against CRC through mechanisms like anti-inflammatory and anti-proliferative properties.
Methods: A comprehensive literature search was conducted in databases such as PubMed and Scopus to identify studies from 2000 to July 2023 on polyphenols and colorectal cancer. We focused on the antioxidant activity, modulation of inflammation and other biological mechanisms of polyphenols.
Results: Polyphenols demonstrate significant potential in the prevention and treatment of colorectal cancer through mechanisms such as antioxidant activity, modulation of inflammatory pathways and regulation of apoptosis. However, variability in research findings highlight the need for further studies to explore their efficacy and interactions in the clinical setting.
Conclusion: This research emphasizes the potential of polyphenols as effective agents in preventing and treatment of colorectal cancer through their antioxidant, anti-inflammatory and epigenetic modulating properties. Further clinical studies are essential to fully understand their mechanisms and demonstrate their efficacy in different populations.

Keywords: polyphenols,colorectal cancer, flavonoids, antioxidant properties, gut microbiota

Introduction

Colorectal cancer (CRC) is a worldwide health issue, causing nearly 700,000 deaths annually, making it the fourth leading cause of cancer-related mortality and the third most common cancer with more than one million new cases diagnosed each year. In terms of gender, CRC is the second most common cancer among women (9%) and the third most common in men. Most cases of colorectal cancer were found in advanced countries (25.1/100.000) compared to developing nations (3.9/100,000) [1]. Similar to other cancers, specific gene mutations can initiate the onset of CRC. These mutations can trigger abnormal cell growth by affecting oncogenes, tumor suppressor genes and genes involved in the DNA repair mechanism. Colorectal cancer can be classified as sporadic, inherited or familial depending the origin of the mutation [2].

Polyphenols are a large group of naturally occurring compounds found in plant-based foods for instance fruits, vegetables, tea, coffee, and wine [3, 4]. These compounds are characterized by their antioxidant properties and their ability to neutralize free radicals and thus prevent cell damage [3, 5]. Polyphenols are divided into several subgroups, including flavonoids, phenolic acids, lignans, and stilbenes [3, 4]. Each class has specific biological activities [3], and together, they are known for their

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role in reducing the risk of various chronic diseases, such as cardiovascular diseases, neurodegenerative disorders, and certain cancers [3, 5]. Their Antioxidant, anti-inflammatory, and anti-proliferative properties make them particularly interesting in the context of cancer prevention and treatment [3, 6].

Several studies on the role of polyphenols in CRC suggest that these molecules have cytotoxic effects on CRC cells and enhance sensitivity to chemo/radiotherapies as well as Inhibition of proliferation, angiogenesis, and metastasis [7]. Various studies on the role of polyphenols in CRC have suggest that these molecules are cytotoxic to CRC cells promote sensitivity to chemotherapy/ radiotherapy and also inhibit proliferation, angiogenesis, and metastasis. While these studies are informative, they have limitations such as small sample size, heterogeneity of polyphenols used, and lack of robust clinical trials. These gaps highlight the need for further research to determine the efficacy and safety of polyphenols in the human population [7, 8].

Epidemiologic studies suggest that a polyphenol- rich diet is associated with a lower incidence of colorectal cancer, possibly due to its anti-inflammatory, anti-proliferative, and pro-apoptotic effects on cancer cells [9-11].

Experimental studies have demonstrated that polyphenols, such as curcumin, epigallocatechin gallate (EGCG), and resveratrol, can inhibit multiple stages of colorectal carcinogenesis by targeting key molecular signaling pathways, including Wnt/β-catenin, NF-κB, and PI3K/Akt signaling [11-13]. In addition, albeit on a limited scale, clinical trials have begun to explore the potential of these compounds as adjunctive agents for the prevention and therapy of colorectal cancer, with promising but preliminary results [11, 13, 14].

Despite these encouraging results, the exact mechanisms of action and clinical relevance of polyphenols in CRC prevention are not yet fully understood and further research is needed [12, 15, 16].

This study therefore investigates how dietary polyphenols affect colorectal cancer risk, attempting to determine the actual effects of certain polyphenols, as other studies have focused on the anti-cancer properties of polyphenols [7, 8, 17].

Materials and Methods

A comprehensive literature search was conducted to identify studies published between 2000 and September 22, 2024, that examined the impact of polyphenols on colorectal cancer and their potential role in prevention and treatment. The search was conducted in electronic databases such as PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar Employing relevant keywords including “polyphenols”, “colorectal cancer”, “flavonoids”, “phenolic acids”, “dietary polyphenols”, “cancer prevention”, “gut microbiota”, and “antioxidant properties”, either independently or combined with “OR” and/or “AND”.

In addition, reference lists of identified studies, related research projects, conference abstracts, dissertations, and relevant reviews were screened as gray literature to ensure comprehensive coverage of all eligible studies. The search strategy aimed to retrieve all relevant articles, encompassing randomized controlled trials, cohort studies, case–control studies and cross-sectional studies. The titles and abstracts of retrieved articles were screened for relevance, and the full texts of potentially eligible articles were thoroughly reviewed for inclusion in the study. Data extraction and quality assessment were performed independently by two reviewers, with any discrepancies resolved through discussion or consultation with a third reviewer. All relevant articles were imported into EndNote X7 software (Thomson Research Soft, Philadelphia, PA) to manage references, and duplicate studies were removed.

Inclusion and exclusion criteria

For this review, the abstracts were initially screened to exclude studies not relevant to the topic. Subsequently, full-text articles were then screened for eligibility, focusing on those available in English that provided detailed information on the biological properties of polyphenols and their effects on colorectal cancer. Studies were included if they explored the relationship between polyphenol intake and the occurrence or progression of colorectal cancer, explored the mechanisms through which polyphenols may exert chemo preventive or therapeutic effects, and compared the efficacy of polyphenols with conventional treatments or preventive strategies for CRC.

Studies were excluded if they were duplicates, did not meet the inclusion criteria or did not provide sufficient information on the role of polyphenols in the prevention and treatment of colorectal cancer.

Data extraction

Two independent reviewers performed the data extraction using a standardized form. The extracted information included the general characteristics of each study, such as the first author’s name, year of publication, and study design, as well as the primary outcomes related to polyphenols and colorectal cancer. Disagreements between reviewers were resolved through discussion and mutual consensus.

Statistical analysis

The main strategy used in the analysis was data synthesis. The heterogeneity of the included studies in terms of study methods and outcome measures made it difficult to perform a meta-analysis. Therefore, the results were presented as qualitative and quantitative syntheses , depending on the type of study.

Results and Discussion

Feng, Feng, Y., et al in (2023) [3] conducted Polyphenol–protein complexes formed by non-covalent or covalent interactions exhibit enhanced antioxidant properties, making them promising for various applications in food systems such as emulsions, gels, packaging films and delivery systems for bioactive compounds. These complexes improve the antioxidant capacity of proteins and protect polyphenols from degradation. Factors such as the type of protein or polyphenol, the

type of combination and the external conditions influence their antioxidant efficacy . Further research is needed to validate their safety and expand the types and sources of proteins and polyphenols for complex formation, which could expand their use in the food industry

Andrés, C. M. C., et al. (2024) [5] conducted Free radicals (FRs) are unstable molecules that cause oxidative stress (OS), damage lipids, proteins, and DNA, and contribute to various diseases and age-related disorders. Antioxidants such as polyphenols, vitamins A, C and E and selenium help to neutralize FRs and reduce their harmful effects. The review highlights the role of these antioxidants in regulating cell metabolism and combating OS-related diseases . It also examines the link between antioxidants and key regulators of aging, such as SIRT1 and NRF2.. Consumption of foods or supplements rich in antioxidants may reduce the risk of chronic diseases and promote overall health.

Dos Santos, F. K. F., et al. (2024) [6] This review explores the antioxidant properties of various natural substances, such as ascorbic acid, green tea polyphenols, and L-glutathione, in mitigating the harmful effects of reduced graphene oxide (rGO), which can cause cell damage , oxidative stress, and inflammation. These antioxidants help neutralize free radicals and protect cellular integrity, making them potential candidates for reducing rGO toxicity. These research findings have significant implications for health, particularly for the prevention of diseases related to oxidative stress, such as cancer and cardiovascular disease. However, further studies are needed to fully understand the therapeutic potential of these natural compounds.

Mileo, A. M., et al. (2019) [7] derived polyphenols in foods may have health benefits in cancer prevention and treatment. They may boost the immune system and work well with other cancer treatments. However, more research is needed to understand how they interact with individual patients' bodies.

Araújo, J. R., et al. (2011) [8] conducted Polyphenols found in fruits and vegetables may help prevent colorectal cancer. They can prevent cancer cells from growing and spreading. However, more research is needed to understand how they work in humans .

Vingrys, K., et al. (2023) [9] conducted a study for more than 35,000 Australians. a small association between the consumption of cereal polyphenols and colorectal cancer risk.

However, more research is needed to understand whether these compounds may protect against other types of cancer.

Fike, L. T., et al. (2022) [10] Black Americans tend to consume less polyphenols than white Americans. One study found that higher polyphenol intake is associated with a lower risk of colorectal cancer (CRC). This was true for all groups studied, regardless of sex, race, income, or body mass index (BMI). The researchers suggest that differences in polyphenol intake may explain why CRC is more common in black Americans.

Núñez-Sánchez, M. A., et al. (2015) [11] conducted Dietary phenolics (such as curcumin, resveratrol) show promise in preclinical studies for the prevention of colorectal cancer (CRC). evidence from clinical trials is limited. Curcumin stands out as a potential adjuvant. The gap between preclinical and clinical results may be due to factors such as inconsistent findings and inadequate dosing. Future research needs to address these challenges to fully evaluate the potential of dietary phenolics in CRC prevention.

White, M., et al. (2014) [12] conducted this study, which systematically reviewed case-control studies investigating the association between polyphenol intake and colorectal cancer (CRC) risk. While some polyphenols (flavanols, procyanidins) were associated with a reduced risk of CRC, the evidence is weaker than suggested by in vitro studies. Inconsistent measurement of polyphenol intake using food-frequency questionnaires may limit the strength of the findings. Future studies may benefit from using objective biomarkers to assess polyphenol intake.

Zamora-Ros, R., et al. (2018) [14] investigated the association between polyphenol intake and colorectal cancer risk in the EPIC cohort. Overall, the total intake of polyphenols was not associated with colorectal cancer risk. However, intake of phenolic acids, which is related to coffee consumption, showed a possible inverse association with colorectal cancer risk in men and a positive association with rectal cancer risk in women.

These findings suggest that the effects of polyphenols on colorectal cancer risk may vary by gender and cancer type. Further studies are needed to confirm these associations and clarify the underlying mechanisms.

Wang, Z. J., et al. (2013) [15] investigated the association between polyphenol intake and colorectal cancer risk in their study. Overall, the total intake of polyphenol was not associated with colorectal cancer risk. However, coffee polyphenol intake was inversely associated with colorectal cancer risk, particularly in distal colon cancer. The association with rectal cancer risk was U-shaped, with the OR decreasing significantly in the second through fourth quintile categories. These results suggest a possible protective effect of coffee consumption against colorectal cancer, particularly colorectal cancer.

Zamora-Ros, R., et al. (2015) [16] stated that this will be the first study to investigate the association between all polyphenol classes and colorectal cancer risk. The EPIC study is particularly suitable for evaluating these associations due to the large number of colorectal cancer cases, the longitudinal study design and the high variability in polyphenol intake among participants in Europe.

Alam, M. N., et al. (2018) [17] The article provides an overview of the anticancer effects of polyphenols in colorectal cancer. It discusses the molecular mechanisms underlying their beneficial effects and highlights the potential of synthetic modifications to improve their efficacy. The review also summarizes clinical trials and preclinical studies evaluating polyphenols for colorectal cancer treatment. Overall, the evidence suggests that polyphenols are promising as chemo preventive agents in colorectal cancer Yao, Z., et al. (2021) argued that curcumin has great potential as a chemo preventive agent in colorectal cancer. In addition, there is evidence that it can be an effective adjunct to colorectal cancer therapy. To

date, few studies have investigated the anti-cancer effects of curcumin formulations and curcumin derivatives in vivo; therefore, further work is needed to confirm their efficacy. In clinical trials, curcumin treatment protocols (formulation, dose and duration) vary from study to study. However, these studies consistently indicate that the preparation is well tolerated and safe, although there is little agreement on its therapeutic efficacy.

Pamplona, B., et al. (2014) [18] investigated the effects of quercetin and genistein on the proliferation of colon cancer cells and their estrogen receptor β (ERβ) expression. The results showed that quercetin and genistein inhibited the proliferation of colon cancer cells expressing ERβ, but not in cells lacking ERβ. This effect was associated with increased ERβ activity and expression. These findings suggest that ERβ plays a crucial role in the antitumor effect of phytoestrogens like quercetin and genistein in colon cancer.

Mechanism

Antioxidant Activity

Polyphenols, such as flavonoids and phenolic acids, have strong antioxidant properties that allow them to neutralize free radicals and reduce oxidative stress. Oxidative stress is a key factor in carcinogenesis, including colorectal cancer [19]. By scavenging reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidant enzymes (e.g., superoxide dismutase, glutathione peroxidase), polyphenols protect cells from DNA damage, lipid peroxidation, and protein oxidation, all of which are implicated in cancer development [19, 20].

Modulation of inflammatory pathways

Chronic inflammation is a well-established risk factor for colorectal cancer. Polyphenols can modulate inflammatory pathways by inhibiting key pro-inflammatory mediators such as nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS)(21). For instance, curcumin, a polyphenol found in turmeric, has been shown to suppress NF-κB activation, leading to decreased expression of COX-2 and pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).

Regulation of apoptosis and cell cycle

Polyphenols can trigger apoptosis (programmed cell death) and inhibit cell proliferation in colorectal cancer cells. They achieve this by modulating various signaling pathways:

-Mitochondrial pathway: Polyphenols like resveratrol and epigallocatechin gallate (EGCG) can trigger [22, 23]. the release of cytochrome c from the mitochondria, which activates the caspases and leads to apoptosis

-The death receptor pathway: Some polyphenols increase the expression of death receptors (e.g., Fas, DR4) on cancer cells, promoting extrinsic apoptotic signaling [24].

-Cell cycle arrest: Polyphenols can induce cell cycle arrest at different checkpoints (G1, S, or G2/M phase) by regulating the expression of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors [25].

Inhibition of cancer stem cells (CSCs)

Cancer stem cells are thought to contribute to the development, progression, metastasis and recurrence of tumors in colorectal cancer. Polyphenols such as curcumin, quercetin and EGCG have been shown to be able to target CSCs by downregulating stem cell markers (e.g. CD133, CD44) and inhibiting the Wnt/β-catenin, Hedgehog and Notch signaling pathways, which are critical for the maintenance of CSCs [26].

Epigenetic modulation

Polyphenols can modulate gene expression through epigenetic mechanisms such as DNA methylation, histone modification and the regulation of non-coding RNAs. For example:

-DNA methylation: polyphenols such as genistein and EGCG can inhibit DNA methyltransferases (DNMTs), leading to reactivation of tumor suppressor genes [27].

-Histone Modification: Resveratrol and curcumin can modulate histone acetylation/deacetylation and thus influence the expression of genes involved in the regulation of the cell cycle and apoptosis [28].

-MicroRNAs (miRNAs): Polyphenols can alter the expression of oncogenic and tumor-suppressive miRNAs, affecting signaling pathways involved in cell proliferation and apoptosis [29].

Inhibition of angiogenesis and metastasis

Polyphenols can inhibit angiogenesis (formation of new blood vessels) and metastasis (spread of cancer cells) by targeting multiple molecular targets:

-VEGF Pathway: Polyphenols such as curcumin and resveratrol inhibit vascular endothelial growth factor (VEGF) and its receptor (VEGFR), which are critical for angiogenesis [30].

-Matrix metalloproteinases (MMPs): Polyphenols inhibit MMPs, enzymes that degrade the extracellular matrix and facilitate metastasis [31].

Modulation of the gut microbiota

The gut microbiota plays an important role in the development of colorectal cancer. Polyphenols can influence the composition and activity of the gut microbiota, leading to the production of beneficial metabolites such as short-chain fatty acids (SCFA), which have a protective effect against colorectal cancer.

The gut microbiota plays an important role in the development of colorectal cancer. Polyphenols can influence the composition and activity of the gut microbiota, leading to the production of beneficial metabolites such as short-chain fatty acids (SCFA), which have a protective effect against colorectal cancer. For instance, polyphenols from berries and tea have been shown to increase the abundance of Bifidobacterium and Lactobacillus, which are associated with anti-cancer properties [32].

Modulation of Wnt/β-Catenin Signaling

The Wnt/β-catenin signaling pathway is often dysregulated in colorectal cancer. Polyphenols such as curcumin and quercetin can inhibit signaling pathways by reducing translocation of the β-catenin core and downstream oncogenic transcriptional activity [33].

Limitations

Although this comprehensive review provides a thorough examination of the potential role of polyphenols in the prevention and treatment of colorectal cancer (CRC), some limitations should be noted:

Heterogeneity of study designs and populations: The studies included in this review differed greatly in their design, populations and methodology. This heterogeneity makes a direct comparison of the results between the studies difficult and limits the ability to generalize conclusions. Furthermore, differences in polyphenol sources, dosages and study duration could contribute to the variability of the outcomes observed results.

Variability in the bioavailability of polyphenols: The bioavailability of polyphenols is influenced by numerous factors, including their chemical structure, food matrix, gut microbiota composition, and individual metabolic differences. Many studies do not take these variables into account, which can significantly influence the efficacy of polyphenols in vivo. This limitation highlights the need for a standardized assessment of bioavailability in future research to better understand the dose-response relationship.

Lack of consistency in measuring polyphenol intake many observational studies rely on self-reported dietary intake data, which may be prone to recall bias and inaccuracies. The use of food-frequency questionnaires and dietary surveys can lead to misclassification of polyphenol intake. Additionally, few studies employ objective biomarkers to validate intake, which would provide more reliable data on the correlation between polyphenol consumption and CRC risk.

Limited evidence from human clinical trials: While numerous preclinical studies demonstrate the anti-carcinogenic potential of polyphenols, clinical evidence remains limited. The majority of human studies are observational, and there are few randomized controlled trials (RCTs) that have examined the effects of specific polyphenols on CRC incidence or progression. This gap in clinical evidence makes it challenging to draw definitive conclusions about the therapeutic potential of polyphenols in CRC prevention and treatment.

Potential confounding factors: Many studies do not adequately account for confounding factors such as diet, lifestyle, genetic predispositions and environmental influences that may also affect CRC risk. These factors can obscure the actual effect of polyphenols and complicate the interpretation of the results.

Insufficient understanding of mechanisms in humans: While the review discusses various mechanisms by which polyphenols may influence CRC (e.g., antioxidant activity, modulation of inflammatory pathways, induction of apoptosis, etc.), much of this evidence comes from in vitro and animal studies. The translation of these findings to human populations remains uncertain, and there is a need for more mechanistic studies involving human subjects to confirm these effects.

Publication bias and selective reporting: There is a possibility of publication bias, as studies with positive results are more likely to be published than those with invalid or negative results. In addition, the search for gray literature may not have included all relevant unpublished studies, potentially biasing the results of the review.

Variation in the composition of the gut microbiota: The influence of polyphenols on the gut microbiota and thus on colorectal cancer risk is an area of growing interest. However, individual differences in microbiota composition may lead to different responses to polyphenol intake, making it difficult to extrapolate results to broader populations. Further research is needed to understand these interactions and their implications for colorectal cancer prevention.

Future studies

Despite promising findings on the role of polyphenols in the prevention and treatment of colorectal cancer (CRC), further research is needed in several areas to strengthen the evidence base and close existing gaps:

Standardization of polyphenol bioavailability studies: Future research should focus on standardizing the measurement bioavailability and metabolism of polyphenols. Differences in the absorption, distribution, metabolism, and excretion of polyphenols can significantly influence their biological activity. The use of biomarkers and advanced analytical techniques to assess bioavailability will provide more accurate dose-response data and help identify the most effective polyphenol forms and doses for CRC prevention.

Large-scale, longitudinal clinical trials: While preclinical and observational studies provide valuable insights, there is a need for more randomized controlled trials (RCTs) to confirm the chemo preventive and therapeutic effects of specific polyphenols in human populations. Future studies should include large, heterogeneous cohorts with long follow-up periods to evaluate the effects of polyphenol consumption on the incidence, progression and survival of colorectal cancer.

Research into synergistic effects with conventional therapies: Investigating the synergistic potential of polyphenols in combination with conventional CRC treatments, such as chemotherapy and radiotherapy, is crucial. Studies should aim to determine whether polyphenols can enhance treatment efficacy, reduce side effects, and improve overall patient outcomes. This research could pave the way for integrative therapeutic strategies that incorporate polyphenols as adjuvant agents.

Mechanistic studies in human subjects: While many of the proposed mechanisms of action, such as antioxidant activity, modulation of inflammatory pathways, and epigenetic modulation, have been demonstrated in vitro and in animal models, there is a need for more mechanistic studies in humans. Investigating these mechanisms in a clinical setting will help validate their relevance and applicability to human health and disease.

Using objective biomarkers to assess polyphenol intake: To overcome the limitations of dietary recalls

and food frequency questionnaires, future studies should use objective biomarkers to assess polyphenol intake and polyphenol metabolism. This approach will allow more accurate estimates of polyphenol exposure and its association with colorectal cancer risk and development.

Elucidate the role of the gut microbiota in polyphenol metabolism: The interaction between polyphenols and the gut microbiota is a promising area for future research. Understanding how different polyphenols influence the composition and activity of the gut microbiota and how these changes affect colorectal cancer risk and response to treatment could lead to personalized dietary recommendations and targeted therapeutic interventions.

Exploring the impact of genetic and epigenetic variability: Individual genetic and epigenetic differences may influence the response to polyphenol intake. Future studies should investigate how genetic polymorphisms and epigenetic changes affect polyphenol metabolism and efficacy in the prevention and treatment of colorectal cancer. This research could contribute to the development of personalized nutritional and therapeutic strategies based on genetic and epigenetic profiles.

Addressing Gender and cancer type differences: Some studies suggest that the effects of polyphenols on CRC risk may differ by gender and cancer site (e.g. colon or rectum). Future research should focus on stratifying results by these variables to provide a more nuanced understanding of the effects of polyphenols on different subpopulations and cancer subtypes.

Investigating new Sources and synthetic derivatives of polyphenols: Given the structural diversity of polyphenols, exploration of new sources and development of synthetic derivatives could reveal more potent and bioavailable compounds. . Future research should also investigate the safety and efficacy of these novel compounds in preclinical and clinical settings to expand their potential application in the prevention and treatment of colorectal cancer.

Dealing with conflicting results and methodological challenges: To reconcile inconsistent findings in the current literature, future studies should strive for methodological rigor and transparency. Standardized protocols for study design, polyphenol quantification, and outcome measurement will be essential to improving the reliability and comparability of research findings.

In conclusion, the research results presented emphasize the significant potential of polyphenols as versatile agents in the prevention and treatment of colorectal cancer.

These natural compounds exhibit robust antioxidant properties, effectively neutralize free radicals and reduce oxidative stress, a key factor in carcinogenesis. In addition, polyphenols modulate inflammatory processes, regulate apoptosis and cell cycle progression, and target cancer stem cells, contributing to their anti-cancer effect.

Furthermore, the epigenetic modulation capabilities of polyphenols offer promising possibilities for reactivating tumor suppressor genes and influencing important regulatory pathways. Their role in inhibiting angiogenesis and metastasis further underlines their therapeutic potential. In addition, polyphenols can have a positive effect on the gut microbiota and promote beneficial metabolites that support gut health.

Despite the encouraging results, further clinical studies are needed to fully elucidate the mechanisms by which polyphenols exert their effects and to demonstrate their efficacy in different populations. Expanding research on the safety and use of different polyphenol sources could pave the way for innovative dietary strategies and supplements for the treatment of colorectal cancer. Overall, the integration of polyphenols into dietary practice could represent a promising approach to reduce the incidence and progression of colorectal cancer and contribute to improved health outcomes.

Author Contribution Statement

All authors contributed equally in this study.

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