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Research Paper

A Review on Polyphenolic Compounds in Cancer

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ABSTRACT

Polyphenolic compounds, which are a variety of bioactive phytochemicals that are commonly present in fruits, vegetables, and plant-based beverages, have received considerable interest due to their potential involvement in the prevention and treatment of cancer. The objective of this review is to offer a thorough examination of the existing literature on the influence of polyphenolic compounds on the initiation and advancement of cancer. The review commences by examining the distinct categories of polyphenols, such as flavonoids, phenolic acids, stilbenes, and lignans, emphasizing their structural heterogeneity and origins. The text provides additional clarification on the mechanisms by which polyphenols demonstrate their anti-cancer properties. These mechanisms include antioxidant activity, modulation of cellular signaling pathways, induction of apoptosis, cell cycle arrest, and inhibition of angiogenesis.

This review highlights the potential of polyphenolic compounds as auspicious agents for cancer management in terms of chemoprevention and therapy. The aforementioned information provides helpful insights on the varied mechanisms of action, presents a comprehensive overview of the existing evidence derived from both epidemiological and experimental studies, and highlights potential avenues for further investigation. Enhancing the comprehension of polyphenols and their influence on cancer could potentially facilitate the creation of innovative approaches for cancer prevention, management, and enhanced patient results.

KEYWORDS: *Polyphenolic compounds, Cancer, Flavonoids, Phenolic acids, Stilbenes, Lignans*

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I. INTRODUCTION

Polyphenolic compounds refer to a diverse group of naturally occurring chemicals that possess multiple phenolic functionalities. The compounds are commonly found in vascular plants. Naturally occurring polyphenols are recognized to possess a diverse array of biological activities [1]. Polyphenols, such as quercetin, are widely distributed in plant-based food sources, encompassing a variety of items such as fruits, vegetables, cereals, fruit juices, tea, wine, and infusions. In contrast, flavanones and isoflavones exhibit specificity towards particular dietary sources. Complex mixtures of polyphenols are commonly found in various food sources. The external tissues of plants exhibit a relatively higher concentration of phenolic compounds in comparison to their internal tissues [2]. Polyphenols have been found to offer substantial protection against the onset of various chronic ailments, including but not limited to cardiovascular diseases (CVDs), cancer, diabetes, infections, ageing, and asthma, as per epidemiological research [3]. Cancer is a pathological condition characterized by the uncontrolled proliferation of certain cells within the human body, which subsequently metastasize to other anatomical regions. The onset of cancer can occur in virtually any region of the human anatomy, comprising a vast assemblage of trillions of cells. Typically, the proliferation of human cells occurs via the mechanism of cell division, resulting in the generation of additional cells to meet the physiological demands of the organism. When cells reach senescence or incur injury, they undergo apoptosis, and are subsequently replaced by newly generated cells. The etiology of cancer is often attributed to genetic alterations that impact three primary categories of genes, namely proto-oncogenes, tumor suppressor genes, and DNA repair genes. The alterations in question are occasionally referred to as "cancer drivers." [4]. The current investigation has emphasized the efficacy and auspicious potential of polyphenols in the treatment of cancer. Polyphenols may be regarded as a potential alternative or efficacious adjunct in the treatment of cancer, offering improved therapeutic outcomes.

1.1 POLYPHENOLS

Polyphenols are a class of secondary metabolites observed in a variety of plant components through natural processes [5]. Polyphenols can interact with oxidants that contain a single electron, thereby impeding the formation of free radicals within biological systems. The single electron oxidation mechanisms are regarded as pivotal stages in which polyphenols function as pharmaceutical agents. [6]. Polyphenols can be classified into different categories depending on the number of phenol rings and the structural elements that connect these rings. The main classifications consist of phenolic acids, flavonoids, stilbenes, and lignans [7].

1.2 PHENOLIC ACIDS

Phenolic acids are widely distributed in diverse food sources and can be categorized into two discrete classes, specifically derivatives of benzoic acid and derivatives of cinnamic acid. Edible plants generally contain low levels of hydroxybenzoic acid, except for certain cultivars like red fruits, black radish, and onions, which may demonstrate concentrations of up to several tens of milligrams per kilogram of fresh weight. Hydroxycinnamic acids exhibit a higher degree of prevalence as a class of compounds when compared to hydroxybenzoic acids. The main constituents of this group are p-coumaric, caffeic, ferulic, and sinapic acids.[8]

1.3 FLAVONOIDS

Polyphenolic compounds have been extensively researched, with flavonoids being the most prominent category. The group displays a fundamental structural configuration consisting of a duo of aromatic rings that are interconnected by a trio of carbon atoms, thus creating a heterocyclic compound that is oxygenated. More than 4,000 distinct varieties of flavonoids have been recognized, with a considerable proportion of them being responsible for the aesthetically pleasing coloration observed in flowers, fruits, and foliage.[9]

1.4 STILBENES Stilbenes are distinguished by the existence of dual phenyl groups that are connected by a methylene bridge comprising of two carbon atoms. The dietary intake of stilbenes in humans is comparatively restricted. Most stilbenes found in plants have antifungal properties and act as phytoalexins. These compounds are produced only in response to injury or infection.

1.5 LIGNANS

Lignans are a group of organic compounds that exhibit a diphenolic structure comprising a 2,3-dibenzylbutane unit, which is formed by the merging of two cinnamic acid residues.[10] Polyphenols are a group of organic compounds that can be found in a diverse range of plant-derived sources, such as fruits, vegetables, cereals, and beverages. The molecules in question are categorized as secondary metabolites and are predominantly produced by plants as a mechanism of protection against ultraviolet radiation and pathogenic attacks. Furthermore, these molecules have the potential to cause bitterness and astringency in various food items. Molecules can act as efficient antioxidants, exhibiting the ability to alleviate the detrimental reactivity of reactive oxygen/nitrogen species that arise as secondary products of metabolic pathways in the human organism. Epidemiological research has demonstrated that polyphenols provide significant protection against the development of a range of chronic conditions, such as cardiovascular diseases (CVDs), cancer, diabetes, infections, ageing, and asthma [11].

II. POLYPHENOLS AS AN ANTICANCER AGENT

Phenol and its analogues have been reported to elicit caspase-dependent apoptotic activity and cytotoxic effects on diverse cancerous cell populations. The antitumor activities of phenolic compounds are mainly attributed to their apoptotic effects, scavenging of radicals, as well as their antioxidant and pro-oxidant properties. Selassie and colleagues have recently conducted quantitative structure-activity relationship studies on the cellular apoptosis and cytotoxicity of phenolic compounds. [12] Cancer ranks as the second most prevalent cause of death globally. In general, there has been an escalation in the incidence of cancer. In the United States, specifically, around 1,665,540 individuals were afflicted with cancer [13]. Therefore, cancer is a serious problem affecting the health of all human societies. Unfortunately, it is a variety disease at the tissue level and this variety is a major challenge for its specific diagnosis, followed by efficacy of treatment. In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus, and thyroid, respectively. This data indicates that prostate and breast cancer constitute a major portion of cancer in men and women, respectively. [14]. Cancer occurs by a series of successive mutations in genes so that these mutations change cell functions. Chemical compounds have an obvious role of forming gene mutations and cancer cells. In addition, smoking involves several carcinogenic chemical compounds that lead to lung cancer [15].

Over the past decade or so, there has been a consistent evaluation and meta-analysis of the correlation between the intake of polyphenols and the incidence of cancer. The consumption of isoflavones was found to be linked with a 19% decrease in the likelihood of developing gastric cancer, as per the results of a meta-analysis conducted on prospective studies [16]. Recent epidemiological research has suggested that the consumption of soy products may be associated with a reduction in the risk of breast cancer [17]. The ingestion of isoflavone and flavanol exhibited a statistically significant association with a projected 30% decline in the occurrence of ovarian and endometrial malignancies in both cohort and case-control investigations. The consumption of soy isoflavones and soy-based foods has been linked to a decreased likelihood of developing colorectal cancer in two meta-analyses conducted on Asian populations. The first meta-analysis, which included 13 case-control studies and four prospective studies, demonstrated a 23% decrease in risk. The findings of a case-control survey conducted in Korea suggest that a significant association exists between a high consumption of total soy products and a decreased risk of colorectal cancer, particularly at the distal and rectal sites. [18]. This review focuses on the compounds that show anticancer properties.

2.1 QUERCETIN

Quercetin, a polyphenol, is abundantly present in nature and belongs to the flavanol class (3,3',4',5,7-pentahydroxyflavone). Quercetin is a flavonoid that is present in various plant components such as leaves, grains, and fruits. It is also a constituent of certain food items and beverages, such as tea and red wine [19]. Quercetin has been found to possess a diverse array of biological properties, such as antioxidant, antimicrobial, anticarcinogenic, antidiabetic, and anti-inflammatory activities. At low concentrations, Quercetin serves as an antioxidant and elicits chemo preventive effects. Nevertheless, elevated concentrations of quercetin demonstrate pro-oxidant properties and could potentially induce a chemotherapeutic response [20]. The present study assessed the growth inhibitory effects of quercetin and the antineoplastic drug 5-fluorouracil (5-FU) on HepG2 and SMCC-7721 (human hepatocellular carcinoma cell line). Quercetin exhibited a dose-dependent effect on the inhibition of cell growth in both cell lines, and also resulted in an increase in the efficacy of 5-FU. Moreover, quercetin alters the expression of proteins that are dependent on apoptosis, diminishes the expansion of tumors, and augments the output of 5-FU in the mouse xenograft model [21]. The study reveals that Quercetin has the potential to induce apoptosis and inhibit hypoxia-induced 5' adenosine monophosphate-activated protein kinase (AMPK) activity in HCT116 cells, which are a human colon cancer cell line. The BGC-823 cell line, which is derived from human gastric cancer, exhibited notable morphological alterations following treatment with quercetin. These changes included detachment, chromatin condensation, cellular shrinkage, rounding, and a condensed nucleus. In contrast, the administration of quercetin to BC3, BCBL1, and BC1 cells (primary effusion lymphoma cell line) resulted in apoptosis induction. This effect was attributed to the inhibition of the PI3K/AKT/mTOR pathway, Wnt/β-catenin pathway, and signal transducer and activator of transcription 3 (STAT3) activation, as well as autophagy in PEL cells [22]. The results of the study indicate that quercetin exhibited a dose-dependent inhibition of cell viability, induced an early apoptotic population, and caused G2/M phase cell cycle arrest in LM3 cells, which are a human hepatocellular carcinoma cell line. Moreover, it impeded the activation of the Janus kinase 2 (JAK2)/STAT3 pathway, curbed migration, and invasion, suppressed tumor growth, and stimulated autophagy via upregulation of LC3B and downregulation of p62 [23]. The findings of these studies suggest that quercetin exhibits significant anticancer properties by impeding cellular proliferation, instigating apoptosis, and inducing cell cycle arrest in various cancer cell lines. Therefore, quercetin can be considered a potent agent for the treatment of cancer.

2.2 CURCUMIN

Curcumin, a hydrophobic polyphenol with a bright-yellow hue, is found in the rhizome of Curcuma longa, a perennial herb belonging to the family Zingiberaceae [24]. Curcumin, a polyphenolic compound, has demonstrated therapeutic advantages in various chronic ailments such as arthritis, neurodegenerative disorders, metabolic syndrome, liver disease, obesity, inflammation, and multiple cancer types [25]. Curcumin has been demonstrated to possess noteworthy properties of anti-inflammatory, antioxidant, anticoagulant, antimutagenic, anticarcinogenic, and anti-infective nature. The therapeutic potential of curcumin has been observed in the context of wound healing. Subsequently, there has been a surge in scientific inquiry regarding the potential utilization of curcumin for promoting health advantages [26]. According to recent research, curcumin has the potential to inhibit proliferation and trigger apoptosis in HT-29 cells (a human colon cancer cell line) via the mitochondrial cell death pathway. The administration of curcumin results in a reduction of Bcl-xL/Bad and Bcl-2/Bax ratios, which is accompanied by the activation of caspase-3 [27]. The administration of curcumin to human T-leukemia cell lines, namely CEM, HSB2, Jurkat, and Molt-4, resulted in a growth inhibition that was dependent on the dosage. Additionally, curcumin induced apoptosis, inhibited PI3K/AKT, and led to the release of cytochrome c, poly (ADP-ribose) polymerase (PARP), and cleaved caspase-3. Likewise, the exposure of curcumin to A549 cells, which is a human non-small lung cancer cell line, hindered cell proliferation, triggered

apoptosis, increased caspase-3 activity, upregulated miR192-5p, and suppressed the PI3K/AKT signaling pathway [28]. Various mechanisms have been observed in in vivo experiments indicating that curcumin sensitizes TRAIL-resistant LNCaP cells, which is a human prostate cancer cell line. The aforementioned substance induces death receptors, increases the expression of proapoptotic Bax members and Bak, reduces the levels of antiapoptotic Bcl-xL proteins, and additionally impedes the activation of VEGF, MMP-2, and MMP-9, which are crucial factors in the processes of metastasis, invasion, and angiogenesis [29].

2.3 RESVERATROL

Resveratrol, a polyphenolic compound known as 3,5,4'-trihydroxystilbene, is a naturally occurring stilbene present in various plant sources such as berries, grapes, and peanuts [30]. Resveratrol possesses various properties such as antioxidative, cardio-protective, estrogenic/anti-estrogenic, anti-inflammatory, and antitumor effects. The compound in question is widely recognised for its ability to exhibit anticancer properties [31]. Numerous laboratory investigations have indicated that resveratrol provides support for a diverse range of medical conditions, such as cardiovascular ailments (CVDs), diabetes, obesity, cancers, hepatic disorders, Parkinson's disease, and Alzheimer's disease. Resveratrol has demonstrated protective properties against a diverse range of malignancies, including but not limited to breast, prostate, colorectal, lung, ovarian, cervical, hepatic, and gastric cancer [32]. The growth of cells with SGC7901, a human gastric adenocarcinoma cell line, is inhibited in a dose-dependent manner by resveratrol. Additionally, resveratrol triggers apoptosis and elevates reactive oxygen species (ROS) levels. The administration of Resveratrol to SGC7901 cells resulted in the induction of DNA damage, as evidenced by increased levels of γ-H2AX, and a decrease in ku70, as determined by Western blot analysis [33]. The administration of resveratrol to TRAMP-C1, TRAMP-C2, and TRAMP-C3 cell lines, which are murine prostate cancer cells, resulted in the induction of caspase-dependent apoptosis through mitochondrial mediation. Additionally, resveratrol treatment led to an upregulation of γ-H2AX expression by enhancing the sensitivity of DNA damage [34]. The administration of resveratrol to SCC-VII, SCC-25, and YD-38 cell-lines, which are associated with oral squamous cancer, has been found to impede cellular proliferation, induce G2/M phase cell cycle arrest through the regulation of cell cycle proteins, and trigger apoptosis [35]. The administration of resveratrol to A375SM cells, a human malignant melanoma cell line, resulted in the arrest of the G2/M phase of the cell cycle, increased generation of reactive oxygen species (ROS), and induction of endoplasmic reticulum (ER) stress, ultimately leading to apoptosis. [36]

2.4 KAEMPFEROL

Kaempferol, a flavonoid compound with the chemical formula 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is present in a variety of commonly consumed fruits and vegetables such as broccoli, beans, gooseberries, kale, strawberries, grapes, citrus fruits, brussel sprouts, tomatoes, grapefruits, and apples. It is also extracted from tea [37]. Several medicinal plants, including Acacia nilotica (L.), Aloe vera (L.), Crocus sativus (L.), Ginkgo biloba (L.), Hypericum perforatum (L.), Phyllanthus emblica (L.), Ribes nigrum (L.), and Rosmarinus officinalis (L.), have been acknowledged for their therapeutic properties.[38] Kaempferol and its glycosylated derivatives exhibit a range of beneficial properties, including neuroprotection, cardio protection, antidiabetic effects, anti-inflammatory activity, antitumor effects, antioxidant activity, antimicrobial activity, and anticancer properties [39]. The compound Kaempferol elicits antiproliferative effects on OVACAR-3 cells, a human ovarian cancer cell line, and exerts an impact on cell viability. Moreover, there was an increase in the percentage of apoptosis in a concentration-dependent manner, which was corroborated by the modulation of apoptotic proteins such as cleaved caspase-3 and cleaved caspase-9. The compound Kaempferol has been found to induce inhibition of the signaling pathways involving PI3K/AKT/mTOR and STAT3 [40]. The administration of kaempferol has been observed to induce apoptosis in HT-29 cells, which are a type of human colon cancer cell line. This effect is mediated through both extrinsic and intrinsic pathways, and is accompanied by alterations in the expression of Bcl-2 family proteins. These changes ultimately result in mitochondrial membrane depolarization and the release of cytochrome c from the mitochondria. Within the cytosol, cytochrome c triggers the activation of caspase-9, which subsequently facilitates the activation of caspase-3 [41]. The induction of autophagy in HepG2, a human hepatocarcinoma cell line, was observed as a result of the upregulation of Atg5, Atg7, and Beclin1 proteins upon exposure to kaempferol. The study demonstrated that via the ER stress- C/EBP homologous protein (CHOP) pathway, there was a dose- and time-dependent promotion of conversion from LC3B I to LC3B II [42]. The administration of kaempferol to HT-29 (a cell line derived from human colon cancer) has been observed to impede cellular proliferation and prompt G2/M cell cycle arrest. This effect is achieved through the modulation of cell cycle proteins in a time-dependent manner [43]. The exposure of U-2 OS cells, which are a human osteosarcoma cell line, to kaempferol has been observed to result in a concentration-dependent inhibition of invasion, migration, and adhesion. The compound in question exhibits a reduction in the activities of MMP-2, MMP-9, and uPA [44]. Additionally, it impedes the DNA-binding activity of activator protein-1 (AP-1) and hinders the activation of MAPKs in U-2 OS cells. In a dose-

dependent manner, the application of kaempferol to SCC-4 cells (a human tongue squamous cell cancer cell line) resulted in the inhibition of cell migration and invasion. Moreover, it has been observed that the compound suppresses AP-1 activity, diminishes MMP-2 expression, reduces ERK1/2 phosphorylation, and exhibits promising antimetastatic properties [45].

TABLE. 1: The anti-cancer properties of specific polyphenols through in vitro and in vivo experimentation.

Name of polyphenols	Type of Cancer	Cell type	Effect	Reference
Quercetin	Hepatocellular cancer	HepG2, SMMC-7721	The induction of apoptosis has been observed to result in a reduction in tumor growth.	[46]
	Breast cancer	MCF-7	Induction of apoptosis	[47]
	Colon cancer	HCT-116	Apoptosis-inducing	[48]
	Gastric cancer	BGC-823	Inducing apoptosis	[49]
	Pancreatic cancer	PATU-8988, PANC-1	Preventing the spread of cancer and targeting the STAT3 signaling pathway.	[50]
	Prostate cancer	PC-3	Preventing angiogenesis and development of tumors	[51]
Curcumin	Colon cancer	HT29	Inducing apoptosis	[52]
	Lung cancer	A549	The induction of programmed cell death, as well as the inhibition of the PI3K/AKT signaling pathway.	[53]
	Colon cancer	HCT116, SW620	Induce autophagy	[54]
	Pancreatic cancer	PANC1, BxPC3	The effects of G2/M cell cycle arrest, apoptosis, and autophagy.	[55]
	Gastric cancer	AGS	G2/M phase cell cycle arrest, apoptosis, Ras/ERK pathway	[56]
	Prostate cancer	DU145	The act of impeding the spread of cancer cells to other parts of the body (Inhibiting metastasis)	[57]
Resveratrol	Gastric cancer	SGC7901	Inducing Apoptosis	[58]
	Prostate cancer	TRAMP-C1, TRAMP-C2, & TRAMP-C3	Inducing Apoptosis	[59]
	Oral cancer	SCC-VII, SCC-25 & YD-38	The induction of G2/M cell cycle arrest and apoptosis.	[60]
	Hepatocellular cancer	MHCC97-H	Autophagy & hinder the PI3K/AKT pathway.	[61]
	Breast cancer	MDA-MB-231	The induction of apoptosis and inhibition of angiogenesis in vivo.	[62]
Kaempferol	Ovarian cancer	OVACAR-3	The induction of apoptosis and inhibition of the PI3K/AKT/mTOR and STAT3 signaling pathways.	[63]
	Colon cancer	HT-29	Inducing Apoptosis	[64]
	Gastric cancer	AGS, SNU-638	The activation of autophagy, the IRE1-JNK-CHOP pathway, and the AMPKα/ULK1 pathway.	[65]

III. CONCLUSION

The present review emphasizes the noteworthy contribution of polyphenolic compounds in the prevention and treatment of cancer. Polyphenols, which are obtained from different plant sources, demonstrate a wide range of bioactive characteristics that contribute to their anti-cancer effects. The literature that has been reviewed suggests that these compounds possess the ability to regulate various cellular pathways that are implicated in the advancement and onset of cancer. Despite the encouraging results, numerous obstacles necessitate attention in forthcoming investigations. Ensuring consistent outcomes necessitates the standardization of polyphenol composition, dosage, and delivery systems. Further research is necessary to confirm the effectiveness and safety of polyphenol-based interventions in the management of cancer through clinical trials with increased sample sizes and extended durations.

This review highlights the potential of polyphenolic compounds as a promising addition to the therapeutic arsenal against cancer. Polyphenols exhibit a variety of mechanisms of action and demonstrate synergistic effects with conventional therapies, which presents a promising avenue for future research. Further exploration of the bioavailability, metabolism, and appropriate dosage of polyphenols will advance our

comprehension of their therapeutic capacity. In conclusion, the utilization of polyphenols has the potential to pave the way for innovative approaches to cancer prevention, management, and enhanced patient prognoses.

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