IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

POLYPHENOLIC COMPOUND USED IN THE TREATMENT OF CANCER-A REVIEW

[1]Lakhyajit Borah, [2]Izaz Hussain, [3]Pallabi Bhuyan, [4]Kangkan jyoti saud,

[5]Bidyut Jyoti Krishna Boruah

[1] Assistant Professor,[2]Assistant Professor,[3]Assistant Professor,[4]Assistant Professor,[5]Assistant Professor

[1,2,3,4,5]School of Pharmacy

[1,2,3,4,5]Arunachal University of Studies,Namsai,India

Abstract: Cancer remains a global health challenge, with its complex etiology and limited treatment options. In recent years, there has been growing interest in the potential therapeutic benefits of polyphenolic compounds derived from various natural sources. This comprehensive review aims to provide an overview of the role of polyphenols in cancer treatment.Polyphenols, found abundantly in fruits, vegetables, tea, and other dietary sources, have demonstrated a wide range of bioactive properties, including antioxidant, anti-inflammatory, and anti-cancer effects. Numerous studies have investigated the mechanisms by which polyphenols exert their anti-cancer activities, including modulation of cell cycle progression, induction of apoptosis, inhibition of angiogenesis, and suppression of metastasis.

This review will highlight the major classes of polyphenols, such as flavonoids, phenolic acids, and resveratrol, and their specific effects on various cancer types. Additionally, we will discuss the challenges associated with the bioavailability and pharmacokinetics of polyphenols, which may impact their clinical utility. Promising preclinical and clinical studies will be presented, shedding light on the potential of polyphenolic compounds as adjunctive therapies or chemopreventive agents in the management of cancer.

IndexTerms-Polyphenols,Cancer,Phenolic compound,Stilbenes,Lignans

1. INTRODUCTION

A large range of naturally occurring molecules known as polyphenolic compounds are those that have several phenolic functions. Vascular plants frequently contain the chemicals. It is known that naturally occurring polyphenols have a wide range of biological actions [1]. Quercetin and other polyphenols are present in a number of plant-based foods, including fruits, vegetables, cereals, fruit juices, tea, wine, and infusions. However, flavanones and isoflavones have a preference for specific dietary sources. Various food sources frequently include complex polyphenol combinations. Compared to their internal tissues, plants' exterior tissues have a comparatively larger concentration of phenolic chemicals [2]. According to epidemiological research, polyphenols have been proven to provide significant protection against the development of a variety of chronic diseases, including but not limited to cardiovascular diseases (CVDs), cancer, diabetes, infections, aging, and

asthma [3]. A pathological condition called cancer is characterized by the unchecked growth of certain cells inside the body, which then metastasizes to other anatomical sites. Cancer can start in almost any part of the human body, which is made up of a huge collection of trillions of cells. Human cells typically multiply through the process of cell division, which results in the creation of more cells to satisfy the body's physiological needs. Apoptosis is the process through which injured or old cells die and are replaced by newly formed ones. 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

A group of secondary metabolites known as polyphenols have been found in numerous plant components as a result of natural processes [5]. In biological systems, polyphenols can interact with single-electron oxidants to prevent the production of free radicals. The single electron oxidation pathways are thought to be crucial steps in how polyphenols work as drugs. [6]. Based on the amount of phenol rings and the structural components that connect these rings, polyphenols can be divided into various types. Stilbenes, lignans, phenolic acids, and flavonoids make up the major categories. [7]

1.2 PHENOLIC ACIDS

The two distinct families of phenolic acids—derivatives of benzoic acid and derivatives of cinnamic acid—are extensively dispersed in a variety of food sources. Except for few varieties of red fruits, black radish, and onions, which may show concentrations of up to several tens of milligrams per kilogram of fresh weight, edible plants typically contain modest quantities of hydroxybenzoic acid. When compared to hydroxybenzoic acids, hydroxycinnamic acids are more prevalent as a family of substances. P-coumaric, caffeic, ferulic, and sinapic acids make up the majority of this group's chemical composition.[8]

1.3 FLAVONOIDS

Research on polyphenolic chemicals is widespread, with flavonoids being the most studied group. The group exhibits a fundamental structural arrangement that consists of two aromatic rings joined by three carbon atoms, forming an oxygenated heterocyclic molecule. Flavonoids come in more than 4,000 different kinds, with a significant fraction of them being responsible for the aesthetically attractive colors seen in flowers, fruits, and foliage.[9]

1.4 STILBENES

Stilbenes,particularly resveratrol,have been studied for their potential as cancer chemopreventive agents and their role as polyphenolic compounds in cancer prevention and treatment. The majority of stilbenes are phytoalexins with antifungal effects. These substances are only made in response to an injury or an infection.

1.5 LIGNANS

Lignans are a class of chemical compounds with a 2,3-dibenzylbutane unit, a diphenolic structure created by the union of two cinnamic acid residues.[10] Fruits, vegetables, cereals, and beverages are only a few examples of the wide variety of plant-derived foods that contain polyphenols. These compounds, which fall under the category of secondary metabolites, are primarily produced by plants as a defense against pathogens and ultraviolet radiation. Additionally, these molecules have the ability to add bitterness and astringency to a variety of foods. Molecules can function as effective antioxidants, demonstrating the capacity to reduce the reactive oxygen/nitrogen species' harmful reactivity that develops as a byproduct of metabolic processes in the human body. Epidemiological studies have shown that polyphenols significantly reduce the risk of developing a number

of chronic diseases, including cardiovascular diseases (CVDs), cancer, diabetes, infections, aging, and asthma [11].

POLYPHENOLS AS AN ANTICANCER AGENT

On several cancer cell types, phenol and its analogues have been shown to induce caspase-dependent apoptotic activity and lethal effects. The apoptotic effects, radical scavenging, antioxidant, and pro-oxidant characteristics of phenolic substances are primarily responsible for their anticancer activity. Recent quantitative structure-activity connection investigations on the cellular apoptosis and cytotoxicity of phenolic compounds were carried out by Selassie and colleagues[12]. Cancer is the second leading cause of mortality worldwide. In general, the incidence of cancer has increased. Cancer affected approximately 1,665,540 people in the United States alone [13]. As a result, cancer is a severe disease that affects the health of all human communities. Unfortunately, it is a tissue-level variety disease, and this variety is a big problem for its particular diagnosis, followed by therapy efficacy. The prostate, lung and bronchus, colon and rectum, and urinary bladder have the largest percentages of cancer types in men. Breast, lung and bronchus, colon and rectum, uterine corpus, and thyroid cancer are the most common in women. According to the data, prostate and breast cancer account for the majority of cancers in men and women, respectively. [14]. Cancer is caused by a succession of successive mutations in genes that alter cell functioning. Chemical substances clearly play a role in the formation of gene mutations and cancer cells. Furthermore, smoking contains various carcinogenic chemical components that cause lung cancer[15]. Over the last decade or so, there has been a consistent examination and meta-analysis of the relationship between polyphenol intake and cancer incidence. According to the findings of a meta-analysis of prospective studies, consuming isoflavones was associated with a 19% reduction in the risk of developing stomach cancer [16]. Consumption of soy products may be connected with a lower risk of breast cancer, according to recent epidemiological studies [17]. In both prospective and case-control research, the consumption of isoflavone and flavanol showed a statistically significant connection with a projected 30% drop in the prevalence of ovarian and endometrial cancers. In two meta-analyses on Asian populations, soy isoflavone and soy-based food consumption has been associated with a lower risk of colorectal cancer. A 23% reduction in risk was shown in the first meta-analysis, which included 13 case-control studies and four prospective investigations. According to the results of a case-control study carried out in Korea, there is a substantial correlation between increased soy consumption overall and a lower risk of colon cancer, particularly at the distal and rectal sites. [18]. This review focuses on substances with anticancer qualities.

2.1 QUERCETIN

A polyphenol called quercetin, which belongs to the flavanol class and is abundant in nature, is 3,3',4',5,7-pentahydroxyflavone. A flavonoid called quercetin can be found in a variety of plant parts, including grains, fruits, and leaves. Additionally, it is an ingredient in some foods and drinks, including red wine and tea [19].A wide range of biological characteristics, including antioxidant, antibacterial, anticarcinogenic, antidiabetic, and anti-inflammatory activity, have been linked to quercetin. Quercetin functions as an antioxidant and has chemopreventive properties at low concentrations. However, high levels of quercetin exhibit pro-oxidant characteristics and may result in a chemotherapeutic response [20]. The current study examined the effects of quercetin and the anti-cancer medication 5-fluorouracil (5-FU) on HepG2 and SMCC-7721 (a cell line for human hepatocellular carcinoma). Quercetin increased the efficacy of 5-FU and had a dose-dependent effect on the suppression of cell proliferation in both cell lines. In the mouse xenograft model, quercetin also modifies the expression of proteins that are associated with apoptosis, inhibits tumor growth, and increases 5-FU production [21]. According to the study, the human colon cancer cell line HCT116 has the ability to induce apoptosis and suppress hypoxia-induced 5' adenosine monophosphate-activated protein kin (AMPK) activity. The quercetin-treated BGC-823 cell line, which is derived from human stomach cancer, showed noticeable morphological

changes. Detachment, chromatin condensation, cellular shrinkage, rounding, and a condensed nucleus were some of these modifications. But when quercetin was given to BC3, BCBL1, and BC1 cells (a primary effusion lymphoma cell line), apoptosis was induced. This result was ascribed to the suppression of autophagy, the PI3K/AKT/mTOR pathway, the Wnt/-catenin pathway, the activation of STAT3 and the signal transducer and activator of transcription 3 (STAT3) in PEL cells [22]. According to the study's findings, quercetin inhibited cell viability in LM3 cells, a cell line used to study human hepatocellular carcinoma, in a dose-dependent manner, generated an early apoptotic population, and stopped the cell cycle in the G2/M phase. Additionally, it prevented the Janus kinase 2 (JAK2)/STAT3 pathway from being activated, inhibited migration and invasion, stopped tumor growth, and induced autophagy by upregulating LC3B and downregulating p62 [23].According to the results of these research, quercetin inhibits cancer cell lines' ability to proliferate, induces apoptosis, and causes cell cycle arrest, all of which are indications that it has strong anticancer capabilities. As a result, quercetin can be regarded as a powerful cancer treatment.

2.2 CURCUMIN

The rhizome of *Curcuma longa*, a perennial herb in the *Zingiberaceae* family, contains curcumin, a hydrophobic polyphenol with a vivid yellow colour [24]. A polyphenolic substance called curcumin has shown therapeutic benefits for a number of chronic conditions, including arthritis, neurological illnesses,obesity, inflammation, metabolic syndrome, liver disease, and several cancer types [25]. Curcumin is a shown to have notable anti-inflammatory, antioxidant, anticoagulant, and antimutagenic characteristics anti-infective and anti-carcinogenic properties. Curcumin's medicinal potential has been seen in the context of healing wounds. There has since been an increase in scientific research into the possibilities the use of curcumin to provide health benefits [26]. Recent studies suggest that curcumin has the capacity to decrease growth and induce apoptosis in HT-29 cells, a cell line derived from human colon cancer. When curcumin is administered, the ratios of Bcl-xL/Bad and Bcl2/Bax are decreased, and caspase-3 is activated as a result [27]. Curcumin inhibited the proliferation of several human T-leukemia cell lines, including CEM, HSB2, Jurkat, and Molt-4, in a dose-dependent manner. Apoptosis was also brought on by curcumin, which also inhibited PI3K/AKT, released cytochrome c, poly (ADP-ribose) polymerase (PARP), and cleaved caspase-3. Curcumin also inhibited cell growth in A549 cells, a cell line used to study human non-small cell lung cancer, caused apoptosis, elevated caspase-3 activity, raised miR192-5p, and other effects. Curcumin sensitizes TRAIL-resistant LNCaP cells, a cell line from a human prostate cancer, according to a number of pathways seen in in vivo tests. The aforementioned substance also inhibits the activation of VEGF, MMP-2, and MMP-9, which are critical elements in the processes of metastasis, invasion, and angiogenesis [29]. It also induces death receptors, increases the expression of proapoptotic Bax members and Bak, decreases the levels of antiapoptotic Bcl-xL proteins, and increases the expression of proapoptotic Bax proteins and Bak [30]. The naturally occurring stilbene resveratrol, also known as 3,5,4'-trihydroxystilbene, is found in many plant sources, including berries, grapes, and peanuts [30]. The antioxidant, cardioprotective, estrogenic/anti-estrogenic, anti-inflammatory, and anticancer activities of resveratrol are only a few of its many attributes. The aforementioned substance is well known for having anticancer effects [31].

2.3 RESVERATROL

Resveratrol appears to support a wide range of medical problems, including cardiovascular diseases (CVDs), diabetes, obesity, malignancies, hepatic disorders, Parkinson's disease, and Alzheimer's disease, according to numerous laboratory studies. A wide variety of cancers, including but not limited to breast, prostate, colorectal, lung, ovarian, cervical, hepatic, and gastric cancer, have been shown to be protected against by resveratrol [32]. Resveratrol inhibits the proliferation of SGC7901 cells, a human gastric cancer cell line, in a dose-dependent way. Resveratrol also causes apoptosis and raises levels of reactive oxygen species (ROS). Resveratrol was given to SGC7901 cells, and the results showed that elevated levels of -H2AX and a reduction in ku70 show that DNA damage has been induced by Western blot examination [33]. The treatment of TRAMP-C1, TRAMP-C2, and TRAMP-C3 with resveratrol cell lines caused the activation of caspase-dependent apoptosis in mouse prostate cancer cells via mediation by the mitochondria. Additionally, resveratrol therapy increased the expression of -H2AX expression by making DNA damage more sensitive [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

Several commonly consumed fruits and vegetables, including broccoli, beans, gooseberries, kale, strawberries, grapes, citrus fruits, brussel sprouts, tomatoes, grapefruits, and apples, contain kaempferol, a flavonoid compound with the chemical formula 3,5,7-trihydroxy-2-(4-hydroxyphenyl)- 4H-1-benzopyran-4-one. Tea can also be used to extract it [37]. Many medicinal plants have been recognized for their healing abilities, 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.).[38] Numerous positive traits are displayed by kaempferol and its glycosylated derivatives, including neuroprotection, cardioprotection, antidiabetic effects, anti-inflammatory activity, antitumor effects, antioxidant activity, antibacterial activity, and anticancer activities [39]. On OVACAR-3 cells, a cell line used to study human ovarian cancer, the substance kaempferol induces antiproliferative effects and has an effect on cell viability. Additionally, the modulation of apoptotic proteins including cleaved caspase-3 and cleaved caspase-9 revealed a rise in the percentage of apoptosis in a concentration-dependent way. According to research, the chemical Kaempferol inhibits the PI3K/AKT/mTOR and STAT3 signaling pathways. Apoptosis has been shown to be provoked by kaempferol therapy in the human colon cancer cell line HT-29 cells. This action is accompanied by changes in the expression of Bcl-2 family proteins and is mediated by both intrinsic and extrinsic routes. The end outcome of these modifications is the depolarization of the mitochondrial membrane and the release of cytochrome c from the mitochondria. Cytochrome c causes caspase-9 to become active in the cytoplasm, which then makes caspase-3 more likely to become active [41]. The overexpression of Atg5, Atg7, and Beclin1 proteins in response to kaempferol treatment was reported to induce autophagy in HepG2, a human hepatocarcinoma cell line. The research found that the conversion of LC3B I to LC3B II was promoted in a dose- and time-dependent manner by the ER stress-C/EBP homologous protein (CHOP) pathway [42]. It has been noted that giving kaempferol to HT-29 (a cell line generated from human colon cancer) prevents cellular growth and causes G2/M cell cycle halt.Cell cycle proteins are modulated in a time-dependent way to provide this effect [43]. There has been evidence that kaempferol causes a concentration-dependent suppression of invasion, migration, and adhesion in U-2 OS cells, a human osteosarcoma cell line. MMP-2, MMP-9, and uPA activity are all reduced by the substance in question [44]. Additionally, it prevents MAPKs from being activated in U-2 OS cells and inhibits the DNA-binding ability of activator protein-1 (AP-1). The administration of kaempferol to SCC-4 cells—a human tongue squamous cell carcinoma cell line—inhibited cell migration and invasion in a dose-dependent manner. Additionally, it has been noted that the substance inhibits AP-1 activity, decreases MMP-2 production, lowers ERK1/2 phosphorylation, and demonstrates promising antimetastatic effects [45].

TABLE 1: *In-vitro* and *in-vivo* research on the anti-cancer effects of certain polyphenols.

Name of polyphenols	Type of Cancer	Effect on Cell	Action	Reference
Quercetin	Hepatocellular cancer	HepG2, SMMC-7721	The induction of apoptosis has been observed as a result reduction in tumor growth.	46
	Breast cancer	MCF-7	The initiation 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 signalling pathway.	50
	Prostate cancer	PC-3	Preventing angiogenesis and development of tumours	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 signalling 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 signalling 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
Genistein	Breast cancer	MCF-7 cancer cells	Destroy MCF-7 cancer cells	66
	Brain tumors	SK-N-BE2	Decrease AIF, decrease caspase-3, decrease VEGF, decrease FGF2, decrease NF-κB	67
	Skin cancer	B164A5	Reduce Tumor weight, reduce quantity of melanin	68

CONCLUSION

Due to their many modes of action and preclinical efficacy, polyphenolic compounds show potential as a supplementary method in the treatment of cancer. Despite the varied results of clinical studies, continuous research and compound optimization could eventually result in more effective and precise cancer therapies. To realize the full potential of polyphenolic chemicals in the battle against cancer, more study and collaboration between scientists, doctors, and pharmaceutical businesses are required.

This review highlights how promising polyphenolic substances could be as a new tool in the fight against cancer. Future research into polyphenols is encouraged by their diverse modes of action and demonstrated synergistic effects with conventional treatments. Our understanding of polyphenols' medicinal potential will improve as we learn more about their bioavailability, metabolism, and ideal dosage. In conclusion, the use of polyphenols may open the door to novel strategies for the treatment, management, and enhancement of patient prognoses for cancer.

REFERENCES

[1]. W. Tuckmantel, A.P. Kozikowski, L.J. Romanczyk Jr., J. Am. Chem. Soc. 121 (1999) 12073.
[2]. Simon BF, Perez-Ilzarbe J, Hernandez T, Gomez- Cordoves C, Estrella I. Importance of phenolic compounds for the characterization of fruit juices. J Agric Food Sci 1992; 40:1531-5.
[3]. Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. Oxidative medicine and cellular longevity, 2, 270-278.
[4]. https://www.cancer.gov/about-cancer/understanding/what-is-cancer#genes-causing-cancer.
[5]. Nešovi´c, M.; Gaši´c, U.; Tosti, T.; Horvacki, N.; Nedi´c, N.; Sredojevi´c, M.; Blagojevi´c, S.; Ignjatovi´c, L.; Teši´c, Ž.
Distribution of polyphenolic and sugar compounds in different buckwheat plant parts. RSC Adv. **2021**, 11, 25816–25829.
[6]. Phenolic compounds in foods and their effects on human health. II: Antioxidants and cancer prevention, in: M.T. Huang, C.-T. Ho, C.Y. Lee (Eds.), ACS Symposium Series, Vol. No. 507, American Chemical Society, Washington DC, 1992
[7]. Spencer JP, Abd El Mohsen MM, Minihane AM, Mathers JC. Biomarkers of the intake of dietary polyphenols: strengths, limitations and application in nutrition research. Br J Nutr 2008; 99:12-22.
[8]. Shahidi F, Naczk M. Food phenolics, sources, chemistry, effects, applications. Lancaster, PA: Technomic Publishing Co Inc, 1995.
[9]. de Groot H, Rauen U. Tissue injury by reactive oxygen species and the protective effects of flavonoids. Fundam Clin Pharmacol 1998; 12: 249-55.
[10]. Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. Ann Med 1997; 29:95-120.
[11]. Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. Oxidative medicine and cellular longevity, 2, 270-278.
[12]. Selassie, C. D., Kapur, S., Verma, R. P., & Rosario, M. (2005). Cellular apoptosis and cytotoxicity of phenolic compounds: a quantitative structure− activity relationship study. Journal of medicinal chemistry, 48(23), 7234-7242.
[13]. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA: a cancer journal for clinicians. American Cancer Society.2013;63:11-30.
[14]. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. 2016;66:7-30.
[15]. Aizawa K, Liu C, Tang S, et al. Tobacco carcinogen induces both lung cancer and non-alcoholic steatohepatitis and hepatocellular carcinomas in ferrets which can be attenuated by lycopene supplementation. International journal of cancer. 2016;139:1171-81.
[16]. Grosso, G., Godos, J., Lamuela- Raventos, R., Ray, S., Micek, A., Pajak, A.,& Galvano, F. (2017). A comprehensive meta- analysis on dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations. Molecular nutrition & food research, 61(4), 1600930.

[17]. Messina, M. (2016). Impact of soy foods on the development of breast cancer and the prognosis of breast cancer patients. Complementary Medicine Research, 23(2), 75-80.
[18]. Rothwell, J. A., Knaze, V., & Zamora-Ros, R. (2017). Polyphenols: Dietary assessment and role in the prevention of cancers. Current Opinion in Clinical Nutrition and Metabolic Care, 20(6), 512-521.
[19]. Massi, A., Bortolini, O., Ragno, D., Bernardi, T., Sacchetti, G., Tacchini, M., & De Risi, C. (2017). Research progress in the modification of quercetin leading to anticancer agents. Molecules, 22(8), 1270.
[20]. Reyes-Farias, M., & Carrasco-Pozo, C. (2019). The anti-cancer effect of quercetin: molecular implications in cancer metabolism. International journal of molecular sciences, 20(13), 3177.
[21]. Dai, W., Gao, Q., Qiu, J., Yuan, J., Wu, G., & Shen, G. (2016). Quercetin induces apoptosis and enhances 5-FU therapeutic efficacy in hepatocellular carcinoma. Tumor Biology, 37, 6307-6313.
[22]. Granato, M., Rizzello, C., Montani, M. S. G., Cuomo, L., Vitillo, M., Santarelli, R., ... & Cirone, M. (2017). Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways. The Journal of nutritional biochemistry, 41, 124-136.
[23]. Wu, L., Li, J., Liu, T., Li, S., Feng, J., Yu, Q. & Guo, C. (2019). Quercetin shows anti- tumor effect in hepatocellular carcinoma LM3 cells by abrogating JAK2/STAT3 signaling pathway. Cancer medicine, 8(10), 4806-4820.
[24]. Zlotogorski, A., Dayan, A., Dayan, D., Chaushu, G., Salo, T., & Vered, M. (2013). Nutraceuticals as new treatment approaches for oral cancer–I: Curcumin. Oral oncology, 49(3), 187-191.
[25]. Giordano, A., & Tommonaro, G. (2019). Curcumin and cancer. Nutrients, 11(10), 2376.
[26]. Devassy, J. G., Nwachukwu, I. D., & Jones, P. J. (2015). Curcumin and cancer: barriers to obtaining a health claim. Nutrition reviews, 73(3), 155-165.
[27]. Wang, J. B., Qi, L. L., Zheng, S. D., & Wu, T. X. (2009). Curcumin induces apoptosis through the mitochondria-mediated apoptotic pathway in HT-29 cells. Journal of Zhejiang University Science B, 10, 93-102.
[28]. Jin, H., Qiao, F., Wang, Y., Xu, Y., & Shang, Y. (2015). Curcumin inhibits cell proliferation and induces apoptosis of human non-small cell lung cancer cells through the upregulation of miR-192-5p and suppression of PI3K/Akt signaling pathway. Oncology reports, 34(5), 2782-2789.
[29]. Shankar, S., Ganapathy, S., Chen, Q., & Srivastava, R. K. (2008). Curcumin sensitizes TRAIL-resistant xenografts: molecular mechanisms of apoptosis, metastasis and angiogenesis. Molecular cancer, 7(1), 1-13.
[30]. Rauf, A., Imran, M., Butt, M. S., Nadeem, M., Peters, D. G., & Mubarak, M. S. (2018). Resveratrol as an anti-cancer agent: A review. Critical reviews in food science and nutrition, 58(9), 1428-1447.
[31]. Ko, J. H., Sethi, G., Um, J. Y., Shanmugam, M. K., Arfuso, F., Kumar, A. P., ... & Ahn, K. S. (2017). The role of resveratrol in cancer therapy. International journal of molecular sciences, 18(12), 2589.
[32]. Meng, X., Zhou, J., Zhao, C. N., Gan, R. Y., & Li, H. B. (2020). Health benefits and molecular mechanisms of resveratrol: A narrative review. Foods, 9(3), 340.
[33]. Wang, Z., Li, W., Meng, X., & Jia, B. (2012). Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. Clinical and Experimental Pharmacology and Physiology, 39(3), 227-232.
[34]. Kumar, S., Eroglu, E., Stokes III, J. A., Scissum-Gunn, K., Saldanha, S. N., Singh, U. P., ... & Mishra, M. K. (2017). Resveratrol induces mitochondria-mediated, caspase-independent apoptosis in murine prostate cancer cells. Oncotarget, 8(13), 20895.
[35]. Yu, X. D., Yang, J. L., Zhang, W. L., & Liu, D. X. (2016). Resveratrol inhibits oral squamous cell carcinoma through induction of apoptosis and G2/M phase cell cycle arrest. Tumor Biology, 37, 2871-2877.
[36]. Heo, J. R., Kim, S. M., Hwang, K. A., Kang, J. H., & Choi, K. C. (2018). Resveratrol induced reactive oxygen species and endoplasmic reticulum stress-mediated apoptosis, and cell cycle arrest in the A375SM malignant melanoma cell line. International journal of molecular medicine, 42(3), 1427-1435.
[37]. Ren, J., Lu, Y., Qian, Y., Chen, B., Wu, T., & Ji, G. (2019). Recent progress regarding kaempferol for the treatment of various diseases. Experimental and therapeutic medicine, 18(4), 2759-2776.
[38]. Devi, K. P., Malar, D. S., Nabavi, S. F., Sureda, A., Xiao, J., Nabavi, S. M., & Daglia, M. (2015). Kaempferol and inflammation: From chemistry to medicine. Pharmacological research, 99, 1-10.
[39]. Imran, M., Salehi, B., Sharifi-Rad, J., Aslam Gondal, T., Saeed, F., Imran, A., & Estevinho, L. M. (2019). Kaempferol: A key emphasis to its anticancer potential. Molecules, 24(12), 2277.

[40]. Yang, S., Si, L., Jia, Y., Jian, W., Yu, Q., Wang, M., & Lin, R. (2019). Kaempferol exerts anti-proliferative effects on human ovarian cancer cells by inducing apoptosis, G0/G1 cell cycle arrest and modulation of MEK/ERK and STAT3 pathways. J buon, 24(3), 975-981.

[41]. Lee, H. S., Cho, H. J., Yu, R., Lee, K. W., Chun, H. S., & Park, J. H. Y. (2014). Mechanisms underlying apoptosis-inducing effects of Kaempferol in HT-29 human colon cancer cells. International journal of molecular sciences, 15(2), 2722-2737.

[42]. Guo, H., Lin, W., Zhang, X., Zhang, X., Hu, Z., Li, L., & Ren, F. (2017). Kaempferol induces hepatocellular carcinoma cell death via endoplasmic reticulum stress-CHOP-autophagy signaling pathway. Oncotarget, 8(47), 82207.

[43]. Cho, H. J., & Park, J. H. Y. (2013). Kaempferol induces cell cycle arrest in HT-29 human colon cancer cells. Journal of cancer prevention, 18(3), 257.

[44]. Chen, H. J., Lin, C. M., Lee, C. Y., Shih, N. C., Peng, S. F., Tsuzuki, M.,& Yang, J. S. (2013). Kaempferol suppresses cell metastasis via inhibition of the ERK-p38-JNK and AP-1 signaling pathways in U-2 OS human osteosarcoma cells. Oncology reports, 30(2), 925-932.

[45]. Lin, C. W., Chen, P. N., Chen, M. K., Yang, W. E., Tang, C. H., Yang, S. F., & Hsieh, Y. S. (2013). Kaempferol reduces matrix metalloproteinase-2 expression by down-regulating ERK1/2 and the activator protein-1 signaling pathways in oral cancer cells. PLoS One, 8(11), e80883.

[46]. Massi, A., Bortolini, O., Ragno, D., Bernardi, T., Sacchetti, G., Tacchini, M., & De Risi, C. (2017). Research progress in the modification of quercetin leading to anticancer agents. *Molecules*, *22*(8), 1270.

[47]. Tabrez, S., Jabir, N. R., Adhami, V. M., Khan, M. I., Moulay, M., Kamal, M. A., & Mukhtar, H. (2020). Nanoencapsulated dietary polyphenols for cancer prevention and treatment: successes and challenges. *Nanomedicine*, *15*(11), 1147-1162.

[48]. Reyes-Farias, M., & Carrasco-Pozo, C. (2019). The anti-cancer effect of quercetin: molecular implications in cancer metabolism. *International journal of molecular sciences*, *20*(13), 3177.

[49]. Kashyap, D., Garg, V. K., Tuli, H. S., Yerer, M. B., Sak, K., Sharma, A. K., & Sandhu, S. S. (2019). Fisetin and quercetin: promising flavonoids with chemopreventive potential. *Biomolecules*, *9*(5), 174.

[50]. Kim, H. S., Wannatung, T., Lee, S., Yang, W. K., Chung, S. H., Lim, J. S., & Ha, J. (2012). Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of AMPK activity in HCT116 colon cancer. *Apoptosis*, *17*, 938-949.

[51]. Wang, P., Zhang, K., Zhang, Q., Mei, J., Chen, C. J., Feng, Z. Z., & Yu, D. H. (2012). Effects of quercetin on the apoptosis of the human gastric carcinoma cells. *Toxicology in Vitro*, *26*(2), 221-228.

[52]. Kee, J. Y., Han, Y. H., Kim, D. S., Mun, J. G., Park, J., Jeong, M. Y., & Hong, S. H. (2016). Inhibitory effect of quercetin on colorectal lung metastasis through inducing apoptosis, and suppression of metastatic ability. *Phytomedicine*, *23*(13), 1680-1690.

[53]. Giordano, A., & Tommonaro, G. (2019). Curcumin and cancer. *Nutrients*, *11*(10), 2376.

[54]. Akbik, D., Ghadiri, M., Chrzanowski, W., & Rohanizadeh, R. (2014). Curcumin as a wound healing agent. *Life sciences*, *116*(1), 1-7.

[55]. Devassy, J. G., Nwachukwu, I. D., & Jones, P. J. (2015). Curcumin and cancer: barriers to obtaining a health claim. *Nutrition reviews*, *73*(3), 155-165.

[56]. Wang, J. B., Qi, L. L., Zheng, S. D., & Wu, T. X. (2009). Curcumin induces apoptosis through the mitochondria-mediated apoptotic pathway in HT-29 cells. *Journal of Zhejiang University Science B*, *10*, 93-102.

[57]. Jin, H., Qiao, F., Wang, Y., Xu, Y., & Shang, Y. (2015). Curcumin inhibits cell proliferation and induces apoptosis of human non-small cell lung cancer cells through the upregulation of miR-192-5p and suppression of PI3K/Akt signaling pathway. *Oncology reports*, *34*(5), 2782-2789.

[58]. Mohankumar, K., Sridharan, S., Pajaniradje, S., Singh, V. K., Ronsard, L., Banerjea, A. C., & Rajagopalan, R. (2015). BDMC-A, an analog of curcumin, inhibits markers of invasion, angiogenesis, and metastasis in breast cancer cells via NF-κB pathway—a comparative study with curcumin. *Biomedicine & Pharmacotherapy*, *74*, 178-186.

[59]. Rauf, A., Imran, M., Butt, M. S., Nadeem, M., Peters, D. G., & Mubarak, M. S. (2018). Resveratrol as an anti-cancer agent: A review. *Critical reviews in food science and nutrition*, *58*(9), 1428-1447.

[60]. Meng, X., Zhou, J., Zhao, C. N., Gan, R. Y., & Li, H. B. (2020). Health benefits and molecular mechanisms of resveratrol: A narrative review. *Foods*, *9*(3), 340.

[61]. Yu, X. D., Yang, J. L., Zhang, W. L., & Liu, D. X. (2016). Resveratrol inhibits oral squamous cell carcinoma through induction of apoptosis and G2/M phase cell cycle arrest. *Tumor Biology*, *37*, 2871-2877.

[62]. Gong, C., & Xia, H. (2020). Resveratrol suppresses melanoma growth by promoting autophagy through inhibiting the PI3K/AKT/mTOR signaling pathway. *Experimental and Therapeutic Medicine*, *19*(3), 1878-1886.

[63]. Garvin, S., Öllinger, K., & Dabrosin, C. (2006). Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts in vivo. *Cancer letters*, *231*(1), 113-122.

[64]. Ren, J., Lu, Y., Qian, Y., Chen, B., Wu, T., & Ji, G. (2019). Recent progress regarding kaempferol for the treatment of various diseases. *Experimental and therapeutic medicine*, *18*(4), 2759-2776.

[65]. Devi, K. P., Malar, D. S., Nabavi, S. F., Sureda, A., Xiao, J., Nabavi, S. M., & Daglia, M. (2015). Kaempferol and inflammation: From chemistry to medicine. *Pharmacological research*, *99*, 1-10.

[66]. Pawlicka, M. A., Zmorzyński, S., Popek-Marciniec, S., & Filip, A. A., The Effects of Genistein at Different Concentrations on MCF-7 Breast Cancer Cells and BJ Dermal Fibroblasts. *Int. J. Mol. Sci.*, 2022, **23**(20), 12360.

[67]. S. Karmakar, S. R. Choudhury, N. L. Banik, and S. K. Ray, "Combination of N-(4-hydroxyphenyl) retinamide and genistein increased apoptosis in neuroblastoma SK-N-BE2 and SH-SY5Y xenografts," Neuroscience, vol. 163, no. 1, pp. 286–295, 2009.

[68]. C. Danciu, F. Borcan, F. Bojin, I. Zupko, and C. Dehelean, "Effect of the isoflavone genistein on tumor size, metastasis potential and melanization in a B16 mouse model of murine melanoma," Natural Product Communications, vol. 8, no. 3, pp. 1934578X1300800–1934578X1300346, 2013.