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Review Article

The Role of Polyphenol Compounds in the Treatment of Cancer Cells

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Abstract

Cancer remains a second leading cause of deaths and major public health problem. It occurs due to extensive DNA damage caused by ultraviolet radiations, ionizing radiations, environmental agents, therapeutic agents, etc. Among all cancers, the most frequently diagnosed cancers are lung (12.7%), breast (10.9%), colorectal (9.7%), and gastric cancer (7.81%). Natural compounds are most favorable against cancer on the count of their anti-cancerous ability, easy to avail and efficient. Among natural compounds, polyphenols (flavonoids, catechin, hesperetin, flavones, quercetin, phenolic acids, ellagic acid, lignans, stilbenes, etc.) represent a large and diverse group used in the prevention and treatment of cancer. Natural polyphenols are derived from different plant sources and from various medicinal plants including *Petroselinum crispum, Apium graveolens, Flemingia vestita, Phyllanthus emblica,* etc. Natural polyphenols possess antioxidant, anti-inflammation, as well as anti-cancerous activities through multiple pathways, they induce apoptosis in breast, colorectal and prostate cancers, lower the nucleoside diphosphate kinase-B activity in lung, bladder and colon cancers, inhibit cell-proliferation and cell cycle arrest by suppressing the NF-kB pathway in various cancers, etc. The current review summarized the anticancer activities of natural polyphenols and their mechanisms of action.

Abbreviations

Akt pathway:A Serine/Threonine-Protein Kinase pathway; COX-2 :Cyclooxygenase-2; HaCaT :Cultured Human Keratinocyte; HDAC:Histone Deacetylase; MAPK pathway: Mitogen-Activated Protein Kinases pathway (Oestrogen Receptor); NF-kB : *Nuclear factor* kappa-light-chain-enhancer of activated B cell; PARP :Poly ADP Ribose Polymerase; ROS :Reactive oxygen Speciese; STAT-1:Signal Transducer and Activator of Transcription 1.

Keywords: Cancer, Flavonoids; *Phyllanthus emblica;* Lignans; Stilbenes; *Yucca periculosa*

Introduction

Cancer remains a moment driving reason for death all around the globe after heart diseases [1]. Cancer is an uncontrolled division of ordinary cells in the body. Old cells do not demolish and continue to grow in an uncontrolled way, forming new abnormal cells. These strange cells form a mass of tissue called tumor. Cancer may categorize into five major classes namely as carcinoma, leukemia, sarcoma, lymphomas, and central nervous system cancer [2,3]. The most physiological and biochemical reasons of cancer are ionized and ultraviolet radiations, viral infections (e.g., human papilloma virus HPV cause cervical growth), smoking, parasites (e.g., schistosomiasis cause bladder cancer), contamination of meal or beverages (e.g., liver cancer start by aflatoxins), and bacterial infections (e.g., gastric cancer cause by *Helicobacter pylori*) [4]. Among all cancers, the most frequently diagnosed cancers are lung (12.7%), breast (10.9%), colorectal (9.7%), and gastric cancer (7.81%) [5]. In 2012, approximately 8.2 million people died due to cancer globally, which were associated with liver, breast, cervical, lung, prostate and gastric cancer [6].

Pakistan is the seventh-most crowded nation on the planet, like other developing nations, Pakistan face a double burden of diseases with an expanded rate of cancer. Due to weak database of health system, there are no comprehensive registries available regarding many diseases included cancer [7]. The breast cancer ratio in Pakistan is higher than other Asian countries. In the recent years, the rising rates of head and neck cancer (HNC) are observed and positioned as second most predominant cancer after lung carcinoma in males and breast carcinoma in females in Pakistan [8]. This situation forces the scientists to study about its prevention and treatment. Within the two decades, many laboratories start working on natural polyphenols and their anticancer effects on human being. Polyphenols are potential component for the discovery of anticancer drugs. Polyphenols known as those compounds that have an aromatic ring with at least two or more hydroxyl substituents, including functional derivatives (esters, methyl ethers, glycosides etc.), these compounds are isolated from different kind of fruits (e.g., apples, berries, grapes, oranges, etc.), vegetables (e.g., yellow onions, parsley, red peppers, etc.), beverages (e.g., tea, red wine, coffee, etc.) and edible plants. [9-11]. These compounds are water soluble [12] and can be classified into five major classes based on their chemical structure namely as flavonoids, phenolic acids, lignans, stilbenes and other polyphenols. Among of all flavonoids and phenolic acids are the richest [10]. Polyphenol mixes are essential constituents of one the greatest and broadly dispersed group of secondary metabolites in plants [13].

Natural dietary polyphenol compounds may induce their anticancer effects through a variety of mechanisms including the modulation of cell cycle signaling, removal of anti-cancerous agents, antioxidant enzyme activity, apoptosis, and cell cycle arrest (**Figure 1**) [14]. Natural polyphenols modulate the Nrf2 and NF-κB cells [15], an *in vitro* study, shows that polyphenols can significantly affect the MAPK and PI3K cells, which show their participation in cancer cell proliferation [16]. Natural polyphenols, for example, apigenin, resveratrol, genistein, luteolin, and quercetin induced apoptosis in different malignancy cells [17]. Oxidative stress and DNA damage are the most common signals which activate the mitochondrial apoptotic pathway, can rupture the membrane of mitochondria and release the cytochrome C [16].

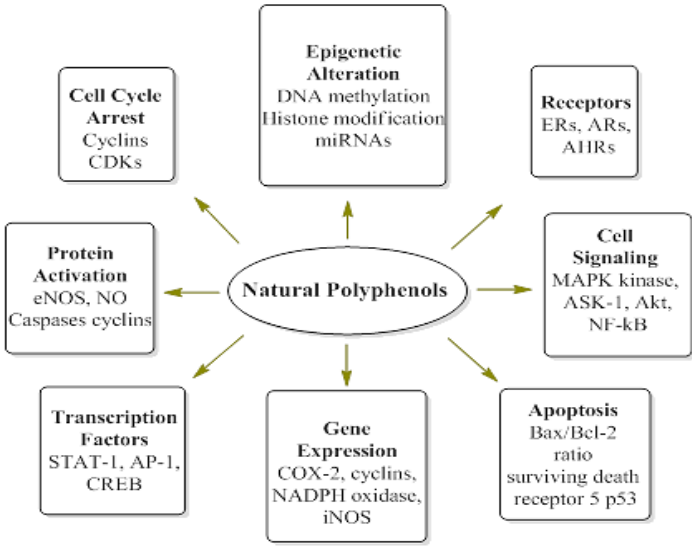

Figure 1: Mechanisms of Natural Polyphenols.

Prevalence of Cancer

Globally, lung cancer accounts 13% of all malignancies analyzed and 27% of all tumors' death [18]. Prostate cancer is most ordinarily analyzed cancer and the second driving reason for death among men, during 2015, 27,540 people died due to prostate cancer in United State. Breast cancer is the second leading cause of deaths in women after lung cancer with the estimation of 231,840 new cases and 40,730 deaths in 2015. Colorectal cancer is the third most leading cause of death with the estimation of 93,090 and 39,610 cases of colon and rectal cancer respectively, and 49,700 deaths in 2015. The incidence of bladder cancer is almost four times higher among men than the women. Just in 2015, 74,000 new cases anticipated that would be analyzed, and 16,000 deaths occur because of bladder cancer [18, 19].

Epidemiological studies of polyphenol compounds are variable, especially when we consider the results of prospective cohort studies (**Table 1**). Zamora-Ros et al. [20] uncovered that the intake of total flavonoids with lignans significantly reduce the thread of colorectal cancer in Spain. Similarly, a study in Montreal, Canada revealed that the high dietary intake of total flavonoids has inverse association with lung cancer threat [21]. A population-based study in America recommended that the high consumption of anthocyanidin (not total flavonoids) may decrease up to 57% of esophageal and gastric cancer [22]. The cohort study of European Prospective Investigation into Cancer and Nutrition (EPIC) revealed that the hepatocellular carcinoma (HCC) risk can be reduced with the intake of flavanols (not total flavonoids), they also observed that total dietary flavonoids are very significant in the reduction of Gastric cancer (GC) risk in women [23,24]. A Cohort study in Netherlands observed that the intake of flavonoids (catechin, epicatechin, kaempferol, myricetin and black tea) significantly reduce the threat of prostate cancer at advanced stage [25]. Badar et al. [26] reported that in Lahore (Pakistan), 15,840 new cancer cases were diagnosed, and 5,134 deaths occurred during 2010-2012, the ratio of male and female patients was 43% and 57% respectively. Akhtar et al. [27] reported that the head and neck (HN) cancer is approximately 8-10% of all cancers in South Asia. According to estimation, the ratio of HN cancer was about 18.74% of all new cancer cases in Pakistan during 2004-2014. Daniyal et al. [28] studied that the stomach cancer risk in Pakistan is low as compared to other countries like US, Japan, etc. Epidemiological data and meta-analysis hardly suggested that when we take diet rich plant polyphenols for long term, they significantly developed our immunity against cancer [29].

Table 1: Dietary Natural Polyphenols Consumption and Cancers risk.

Types of Cancer	Polyphenols	Study Type	Risk Estimation (95% CI)	References
Lung cancer	Flavonoids	case-control study	0.63 (0.47-0.85)	[21]
Prostate cancer	Flavonoids	cohort study	Total catechin 0.73 (0.57-0.95), Kaempferol 0.78 (0.61-1.00), Epicatechin 0.74 (0.57-0.95)	[25]
Breast cancer	Flavonoids	meta-analysis	Flavonols 0.88 (0.88-0.98), Flavones 0.83 (0.76-0.92)	[30]
	Flavanols	cohort study	0.81 (0.67-0.97)	[31]
	Isoflavones	meta-analysis	0.68 (0.52-0.89)	[32]
Colorectal cancer	Flavonoids and Lignans	case-control study	Total flavonoids 0.59 (0.38-0.99); Lignans 0.59 (0.34-0.99)	[20]
	Isoflavones	meta-analysis	0.76 (0.59-0.99)	[33]
HCC	Flavanols	cohort study	0.62 (0.33-0.99)	[23]
Gastric cancer	Flavonoids	case-control study	0.33 (0.15-0.73)	[34]
	Flavonoids	case-control study	No significant association	[22]

Treatment of cancer by natural compounds

Different types of therapies are available to treat the cancer, but they can induce the toxicity and side effects due to their specificity at a single target [35]. Cancer is a multistage disease, so those compounds are required for the prevention and treatment of cancer, which can target the multiple molecular and biochemical pathways without creating any poisonous quality and reactions to ordinary cells [36]. Cancer chemoprevention is the major field in the prevention of carcinomas using different pharmaceutical, synthetic and natural compounds to completely retard, reverse or inhibit the process of carcinomas. Natural compounds are most favored for the treatment of carcinogenesis on the count of their anti-cancerous ability, ease of availability, potential to overcome the resistance, safety, and efficiency [37]. The Plant kingdom are best sources to anti-cancer drugs. Around thirty different anti-cancerous natural mixes have been separated from plants and more than 3,000 species of plants have been accounted in the treatment of cancer and clinical trials so far. Today about 25% of all traditions bear one or more components from plants [38]. Numerous secondary metabolites which are expelled from plant sources represent the potential novel agents by inducing the apoptosis and cell cycle arrest [13]. Among all, natural polyphenol compounds (flavonoids, phenolic acids, lignans, and stilbenes) represent a large and diverse group in the prevention and treatment of cancer [39].

Polyphenols are natural, but synthetic and organic compounds, they always have heteroatom substitutes other than hydroxyl groups. Natural Polyphenol compounds classified into five groups such as flavonoids, phenolic acids, lignans, stilbenes and other polyphenols (Table 2) [10]. These compounds are found almost in all families of plant and can also be isolated from an aquatic submerged plant Myriophyllum spicatum that involved in allopathic interactions [40]. Polyphenols also have ability to bind with the proteins and form soluble and insoluble protein-polyphenol complexes [41].

Table 2: Classification of Natural Polyphenols.

Classification	Represented members		Some common food sources
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin		red, blue, and purple berries; red and purple grapes; red wine
Flavanols	Monomers: Catechin, Epicatechin, Epigallocatechin Epicatechin gallate Dimers and Polymers: Theaflavins, Thearubigins, Proanthocyanidins		Catechins: Teas (particularly green and white), chocolate, grapes, berries, apples Theaflavions and Thearubigins: Teas (particularly black) Proanthocyanidins: Apples, chocolate, red wine, red grapes
Flavanones	Hesperetin, Naringenin, Eriodictyol		Citrus fruits and juices, e.g., oranges, grapefruits, lemons
Flavonols	Quercetin, Kaempferol, Myricetin, Isorhamnetin		Widely distributed in yellow onions, scallions, kale and tea
Flavones	Apigenin, Luteolin		Parsley, thyme, celery, red peppers
Isoflavones	Daidzein, Genistein, Glycitein		Soybeans, soy foods, legumes
Phenolic acids		Hydroxybenzoic Acid	Ellagic acid, Gallic acid Grapes, pomegranates and chocolate
		Hydroxycinnamic Acid	Ferulic acid, Chlorogeni acid Coffee, cereal grains
Lignans	Sesamin, Secoisolariciresinol, Diglucoside		Flaxseeds, sesame
Stilbenes	Resveratrol, Pterostilbene, Piceatannol		Grapes, berries, red wine

This information is taken from the references [9,12]

Typical natural polyphenols and their anticancer activities

Polyphenols are found in foodstuffs and are known to possess anticancer properties; these compounds are derived from secondary metabolites for the protection against predations, ultraviolet radiations, plant pigmentation and reproduction. These mixes are ubiquitous in vegetables, fruits, and drinks [42,43]. Following we will summarize all the classes of natural polyphenols and their anticancer effects:

Flavonoids

Flavonoid is a wide class of polyphenolic compounds; the main sources of flavonoids are fruits, vegetables, seeds, flowers and beverages, different type of foods have enough quantity of anti-cancerous flavonoid (Table 3). The chemical structure of natural flavonoid is diphenylpropane (C6-C3-C6), which contain two aromatic rings at both corner and a three-carbon ring at the center, which forming an oxygenated heterocyclic (Figure 2) [44]. The best-known biological effects of natural flavonoids are prevention against cancer, inhibition of bone resorption, cardio-protective and hormonal action. In addition, they are also more effective against antiviral and antibacterial properties [45,46].

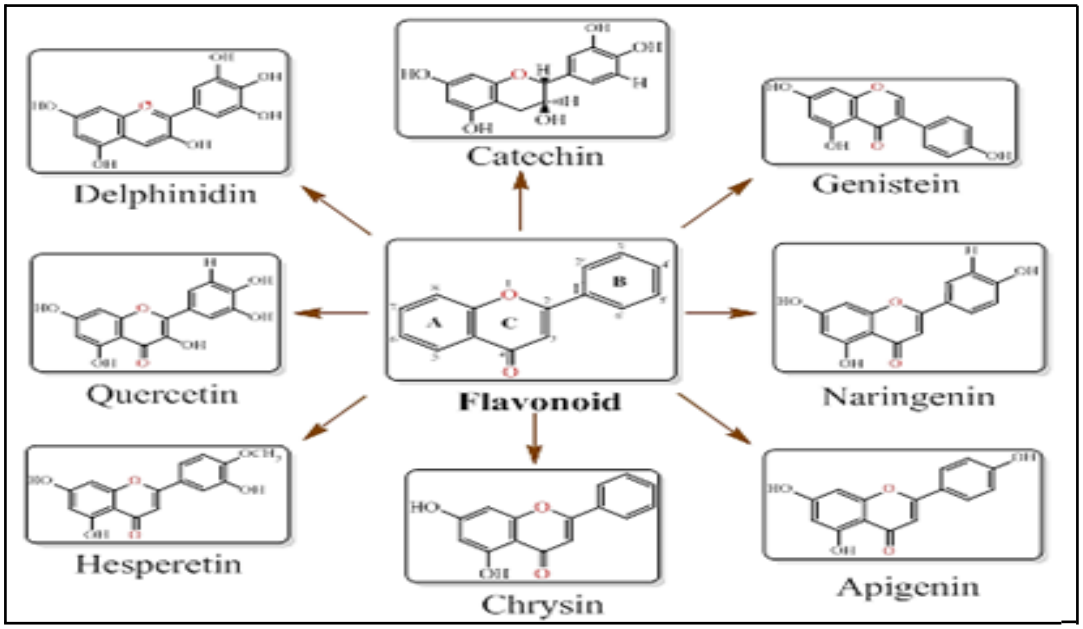

Figure 2: The representative structures of Flavonoid.

Table 3: Foods that contain high amounts of natural Flavonoids.

Description	Class	Subclasses	mg/100g	References
	Flavonols	Kaempferol	0.7	
		Myricetin	2.16	[48]
	Flavones	Apigenin	0.24	
Onions		Luteolin	0.16	
	Flavanones	Naringenin	53	
		Hesperetin	1.5	[49]
Grape fruit, raw	Flavonols	Quercetin	0.5	
	Isoflavones	Genistein	80.99	[50]
Soybeans, mature seeds	Daidzein		62.07	
	Flavan-3-ols	(-)-Epicatechin	99.18	[51]
Cacao beans		(+)-Catechin	88.45	
	Flavones	Apigenin	4503.5	[52]
Spices, parsley, dried (Petroselinum crispum)		Luteolin	19.75	
	Flavan-3-ol	(−)-Epigallocatechin 3-gallete	26.05	
	Flavonols	Quercetin	2.77	[53]
Green tea, brewed, decaffeinated		Kaempferol	1.00	
	Flavan-3-ols	(-)-Epigallocatechin 3-gallate	9.36	
		(+)-Catechin	1.51	[54]
	Flavonols	Quercetin	2.19	
Black tea, brewed, (prepared with tap water)		Myricetin	0.45	

The affinity of flavonoids for cellular membrane depends on the glycosylation and number of hydroxyl groups, substitutive groups also have great impact on their structure, fluidity and permeability. In the metabolism and conjugation of total flavonoids inside the human, the gastrointestinal tract and the colonic micro-flora play an important role and help the total flavonoids into the systematic circulation and liver [47]. Flavonoids can also bind with the ATP-binding sites of assortments of proteins including mitochondrial ATPase, protein kinase A, protein kinase C, calcium plasma membrane ATPase and topoisomerase [44].

Flavanols

Flavanols represent a restricted group of flavonoids, which contain the 2-phenylchromanol skeleton, and can be divided into three main categories monomers, oligomers and polymers. Flavanols are commonly found in fruits, vegetables or some beverages, and shows various biological activities that render them useful for health [55].

Green tea catechins as anticancer drug

Green tea catechins contain (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epigallocatechin gallate (EGCG) [56]. Tea catechins are powerful inhibitors of cell proliferation by inhibiting the acceleration of cells expressing cancer-specific genes, they are also potent inhibitors of cancer metastasis by lowering the nucleoside diphosphate kinase-B activity, due to these activities they have been used for the treatment of lung, bladder, colon, ocular, and cervical cancers which caused by human papilloma virus [57]. Epigallocatechin gallate (EGCG), is one of the most extensively investigated components of green tea, which have numerous advantageous impacts to lessen the tumor and cardiovascular diseases. EGCG founds in dried leaves of green tea (7,380 mg/100g), white tea (4,245 mg/100g), and also found in black tea in very mute quantity (936 mg/100g) [58]. Herbitual green tea intake provides some relief against breast cancer and chemo-prevention in prostate [59].

A study showed that in vitro the EGCG treatment could suppress the nicotine-induced migration and inversion of A549 lung cancer cells [60]. EGCG virtually suppressed the invasion and migration of CL1-5 lung cancer cells by suppressing the matrix metalloproteinase-2 (MMP-2) expression at concentration of 5-20 μM [61]. Banerjee [62] suggested that EGCG and theaflavins (TF) together were assessed for their chemo-preventive potential, these two compounds could activate the caspase-3, caspase-7, and Cox-2 expression, as a result of that, and they lowered the incidence of pre-invasive lung cancer.

Sen et al. [63]; Khan and Mukhtar [64] reported that the Mg2+ plays an important role in increasing the inhibitory effect of EGCG on human DNMT activity. In the context of human cell lines, EGCG (20 μmol/L) inhibits the activity of DNMT in breast (MDA-MB-231 and MCF-7), prostate (PC-3), esophageal (KYSE-150), and colon (HT-29) cancer cells. Chuang et al. [65]; Gilbert and Liu [66] uncovered that the treatment of breast (MDA-MB-231 and MCF-7) cancer cells is performed by the down-regulation of human telomerase reverse transcriptase (hTERT) expression which lead to reduce the telomerase level.

Anthocyanidins

Anthocyanidins are excessively present in the plant kingdom. Red wine, purple cabbage, berries, and grapes are the main sources of anthocyanidins, it is classified into six further classes such as cyanidin, delphinidin, pelargonidin, malvidin, petunidin, and peonidin [67]. It is reported that anthocyanidins can reduce risk of cancer, arthritis, and cardiovascular diseases due to its anti-mutagenesis, antioxidant, and anti-inflammatory activities. A recent study uncovered that the ortho-dihydroxyphenyl structure on the ring number B is responsible to inhibit the growth of tumor and metastasis [68].

Delphinidin as anticancer drug

Among of all anthocyanidins, delphinidin have the highest anticancer activity. Delphinidin suppress the NF-kB pathway to induce apoptosis and cell cycle arrest in several types of cancer [69]. Kausar et al. [70] indicated that the anthocyanidins might show the better role in the combination with other compound than the single one in the treatment of cancer. A study uncovered that the anthocyanidins (peonidin-3-glucoside, cyaniding-3-glucoside and cyanidin-3-O-sambubioside) that are expelled from black rice and the fruit acanthopanax sessiliflorus, could induce the cell-proliferation, apoptosis, and tumor growth of HER2 cells, and inhibit the angiogenesis and invasion in the positive breast cancer [71,72]. Similarly, cyanidin and delphinidin shows the oxidative stress-based cytotoxicity to colorectal cancer cells [72].

Flavonols

The main sources of flavonols (3-hydroxy-2-phenylchromen-4-one) are onions, kale, teas, berries and apples but they are usually present at low concentration, it is further classified into different subgroups namely as quercetin, kaempferols, myricetin and isorhamnetin etc. [73]. Flavonols show their anti-cancer activities through various mechanisms including the antioxidant activity, interactions with proteins, and inhibit the enzymes (CYP2C9 and CYP3A4) that regulates the cancer cells [74].

Quercetin as anticancer drug

Quercetin (2-phenyl-4H-1-benzopyran-4-one, 2-phenylchromone) is a bioactive and predominant flavonol, its chemical structure is responsible for its anti-oxidant activities, the hydroxyl groups that attached at hetertocyclic ring B at carbon 3 and 5 are responsible for its anti-proliferative potential and also give good sensitivity against the free-radicals [36,75]. A study indicated that the daily intake of quercetin in the United States, Europe, and Asia is ranging from 4 to 68 mg per individual [76]. The metabolite of quercetin (quercetin-3-O-glucuronide), have the significant role in inhibition the noradrenaline, which bind with 2-adrenegic by suppressing the DNA damage, that is induced during the treatment of human breast cancer cells (MCF-10A) by noradrenaline and 4-hydrooxyestradiol [77].

The best possible known mechanism of quercetin is not completely found yet, but the least investigated anticancer outcomes of quercetin is highlighted as it could repress the sodium-dependent glucose transporter-1 (SGLT-1), block the cell cycle at several phases (G2/M or G1), and

can go about as a competitive inhibitor of efflux pumps. In short, it promotes the apoptosis [36].

Flavanones

Flavanones (2-phenylchroman-4-ones) are most abundant in the peel and the juices of citrus fruits, and additionally ordered into various subclasses namely as naringenin, hesperetin, eriodictyol, etc. [78]. Flavanones possess many pharmacological properties including antibacterial, antioxidant, anti-fungal and antiVSMCs vegetation activities, and have been reported as a potent anticancer agent [79].

Hesperetin as anticancer drug

Hesperetin belong to class flavanones, mainly founds in citrus fruits included oranges and grapefruits. Hesperetin could reduce the DNMT activity in the nuclear extraction of esophageal squamous cell carcinoma KYSE-510, when it incubated for 1.5h with 20-50 μmol/L [74]. Choi [80] recommended that the hesperetin capture the cell cycle at G_1-stage during the treatment of breast cancer (MCF-7) cells and suppress the activity of cell proliferation in carcinoid cells by expending the Notch-1 expression. Palit et al. [81] uncovered that in the treatment of breast cancer cells, hesperetin (40-200 μM) promote the ROS and ASK1/JNK activation pathways and induce the growth inhibition through mitochondria-mediated apoptosis.

In cervical malignancy cells hesperetin initiated apoptosis through death receptors and mitochondrial pathways [82]. In the prostate cancer PC-3 cells hespeterin (40-90 μM) induced the apoptosis, which are mediated by the NF-κB pathway [83]. Zhang et al. [84] demonstrated that the hesperetin (100-400 μM) induced the apoptosis (mitochondria-mediated) through promoting the ROS accumulation in the treatment of gastric tumor cells.

Flavones

Flavones are a class of total flavonoids with the backbone of 2-phenylchromen-4-one (2-phenyl1-benzopyran-4-one), they are usually found in products of the soil like celery, thyme, parsley, etc., and show their solubility toward water and ethanol. Because of their anti-proliferative, antioxidant, and anti-inflammatory activities, they could diminish the threat of cancer and cardiovascular ailments [78,85].

The anticancer activity of apigenin

Apigenins are derived from some medicinal plants such as *Lycopodium clavatum* (club moss), and from some vegetables, for example, *Apium graveolens* (celery) and *Petroselinum crispum* (parsley) [86]. Recently *in vitro* study reported that apigenin have numerous gainful roles in anti-proliferation properties with the enlistment of apoptosis and cell cycle arrest in the cancer cells, and also shown down-regulation of NF-κB, UV-B-induced ROS, and DNA damage by removing the cyclobutane rings [87].

Apigenin initiated the apoptosis and cell cycle arrest in the treatment of prostate cancer (PC-3 and 22Rv1) cells. The daily dose of apigenin (20-40 mol/L) suppressed the activity of HDAC1 and HDAC3 on protein level and mRNA which resulted the hyperacetylation of histone (H3 and H4) during the treatment of prostate cancer [88]. Apigenin possess the protective effect in epithelial cells from lipopolysaccharide (LPS)-induced inflammation. It holds the DNA damage under wraps by reducing the caspase-3 expression levels and ROS production [89]. Apigenin initiates the ATM and H2AX phosphorylation with the down-regulation of cell cycle controlling and DNA repair genes, which incites the apoptosis/DNA damage in the malignancy cells [90]. Kroonen et al. [91] demonstrated that apigenin control the DNA damage by the activation of NF-κB in malignant glioma cells, inhibition of casein kinase-2, and regulations of cell proliferation. Gates et al. [92] suggested in a population-based examination that ovarian cancer can be overcome by apigenin.

Isoflavones

The main products of Isoflavones are peas, legumes, and alfalfa. Genistein and daidzein are the most prominent isoflavones. Isoflavones shown anticancer activities against leukemia, prostate, breast, colon and lung cancer [93].

The anticancer activity of genistein

Genistein was first isolated from dyer's broom *Genista tinctoria* plant. The main sources are soybeans, fava

beans, and psoralea. Also founds in many medicinal plants like *Flemingia vestita* and *Flemingia macrophylla* [94]. Genistein indicates chemo-therapeutic and chemo-preventive exercises in numerous tumors, particularly in hormone-dependent cancers. The *in vivo* and *in vitro* studies conformed its antineoplastic effects in prostate, breast, urinary, colon, and skin cancer [95]. Tian et al. [96] reported that in lung cancer treatment genistein (25-75 μM) could inhibit the cell proliferation and migration of H446 cell by the induction of cycle arrest at G_2/M-stages and apoptosis. In the prostate malignancy (LNCaP and PC-3) and esophageal squamous cell carcinoma (KYSE-150), genistein repress the DNMT by the reduction of cellular accessibility of SAM with the dose of 20-50 μmol/L [97]. In the breast cancer the conjugates of EGF-genistein could inhibit the EGF-Rc tyrosine kinase and induce the apoptosis, killing approximately 99.99% of clonogenic breast cancer cells [98]. A study revealed that in the treatment (25-100 μM) of colon cancer cells, genistein exhibit pro-apoptosis and anti-proliferative effects [99].

Phenolic acids

Phenolic acids are aromatic acidic compounds and are significant constituent of plants which are derived from a variety of fruits, vegetables, beverages, legumes and from other edible plants. Hydroxybenzoic acid (gallic acids, ellagic acids, etc.) and hydroxycinnamic acid (cinnamic acids, caffeic acids, ferulic acids, etc.) are chief subclasses of phenolic acids (**Figure 3**) [100]. Phenolic acids and its analogues namely as Gallic and caffeic acids, display verities of biological activities, in addition to their antioxidant activities, which are related to regulations of carcinogenesis [101].

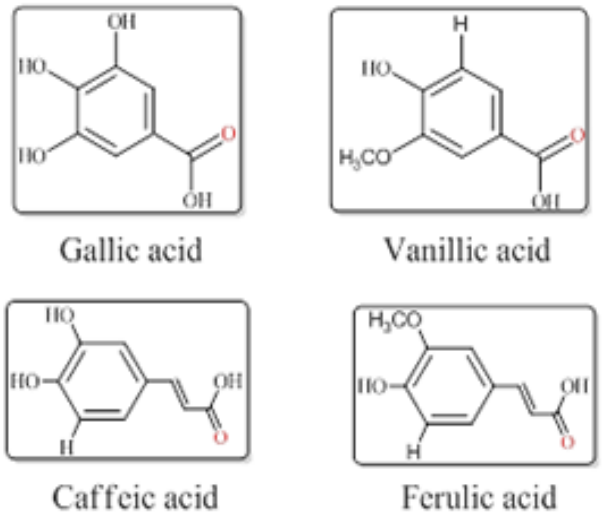

Figure 3: The representative structures of Phenolic acid.

Hydroxybenzoic acids

Hydroxybenzoic acids are available in couple of edible plant and its concentration is exceptionally factor with the utilization of coffee. The derivatives of Hydroxybeznoic acid (protocatechuic, vanillic and p-hydroxybenzoic acids) form p-coumaric and caffeic acid, which have important anticancer activities [102].

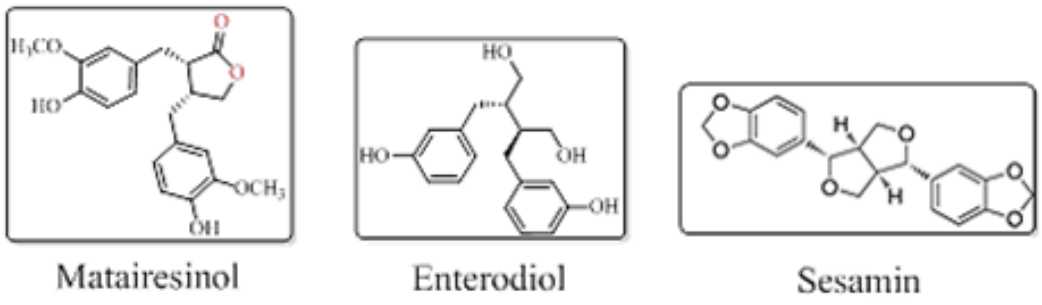

Figure 4: The Chemical structures of lignan derivatives.

Gallic acid as anticancer drug

Gallic acid is widely extracted from plant-based fruits and present in hydrolyzable tannins in minute quantity. It possesses numerous pharmacological (anticancer, antimicrobial and anti-inflammatory) activities, and induced apoptotic in colon cancer cells (HCT-15) [103]. Gallic acids are segregated from *Phyllanthus emblica* fruit, which demonstrated its anti-proliferative exercises against breast

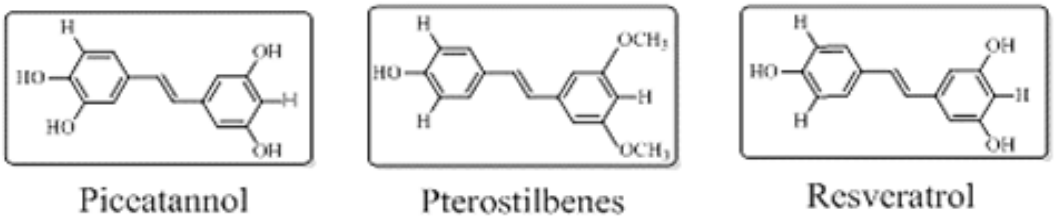

Figure 5: The Chemical structures of Stilbene derivatives.

Anticancer activity of resveratrol:

Resveratrol (3,4,5-trihydroxy-trans-stilbene) is an important polyphenol, berries, grapes, peanuts and other edible plants are the major products of resveratrol. Resveratrol also expelled from the root of *Polygonum cuspidatum* [120]. Resveratrol possess multiple pharmacological, molecular and biochemical properties against precancerous cells. *In vitro* and *in vivo* studies recommended that resveratrol have properties against a variety of human ailments, including cardio and neuro-protection, invulnerable direction, and cancer chemoprevention [122]. Resveratrol prompted apoptosis and cell cycle arrest in precancerous or cancer cells by controlling the different signal pathways, including Akt, MAPK, Wnt, etc., without effecting the normal cells [123]. In the treatment of gastric cancer cells, resveratrol (20-50μM) actuated the cell cycle capture at G_1 stage [124]. In the chemo-resistant human colon cancer cells, resveratrol (50-400μM) used for 30 minutes as anticancer drugs, which induce apoptosis via CD95 and Wnt pathways [125]. In the breast cancer, resveratrol induced apoptosis in MCF-7 and casp-3 cells [126]. Some cancers and their pathways are enlisted in **Table 4**.

Table 4: Resveratrol involved in different pathways against multiple Cancers.

Cancers	Pathways	References
Breast cancer	CD95	[127]
Colon cancer	CD95, Wnt	[128]
Lung cancer	NF-κB, SIRTI	[129]
Prostate cancer	NF-κB	[130]
Lymphocytes	CD95	[123]
Skin cancer	Apoptosis, NF-Kb	[131]

cancer cells. In stomach adenocarcinoma, gallic acids (3.5 μM) reduce the tumor metastasis by inhibiting the activities of NF-κB and down-regulation of PI3K/AKT cells [104]. In leukemia, gallic acid showed pro-apoptosis activities by the production of hydrogen peroxide (H_2O_2) [105]. Zhao and Hu [106] reported that gallic acid (10-40 μg/ml) significantly reduce the cell-proliferation, invasion and angiogenesis HTB-35 and HeLa in the treatment of cervical cancer. Forester et al. [107] demonstrated that in the treatment of colon cancer cells (Caco-2) gallic acid induce apoptosis and cell cycle rest at G_0/G_1 stage by inhibiting the transcriptional factors (STAT-1, NF-kB and OCT-1).

Hydroxycinnamic acids

Hydroxycinnamic acids belong to the class aromatic acids and classified into many subgroups such as caffeic, cinnamic, chlorogrnic, coumeric, sinapic and ferulic acids. In cancer cells they showed inhibitory cell-proliferation activity [108].

Table 5: Natural Polyphenols as Anticancer in the in vivo and in vitro studies.

Polyphenols/ Cancer Type	Study Type	Dose	References
Breast cancer			
EGCG	*in vitro*	1–40 μM	[135]
Hesperetin	*in vitro*	40–200 μM	[81]
Chrysin	*in vitro*	5–20 μM	[136]
Quercetin	*in vitro*	1–200 μM	[137]
Luteolin	*in vitro*	10–40 μM	[94]
Daidzein	*in vitro*	3–50 μM	[138]
Genistein	*in vitro*	5–20 μM	[139]
Genistein	*in vivo*	≤ 500 ppm	[140]
Ellagic acid	*in vitro*	10–40 μg/mL	[141]
Ellagic acid	*in vivo*	50–100 mg/kg	[94]
Lung cancer			
Anthocyanidins	*in vivo*	0.5 mg/mouse	[70]
Xanthohumol	*in vitro*	14–42 μM	[142]
EGCG	*in vitro*	5–20 μM	[61]
Naringenin	*in vitro*	100 μM	[143]
Luteolin	*in vivo*	10–30 mg/kg	[144]
Genistein	*in vitro*	25–75 μM	[96]
Resveratrol	*in vitro*	5–50 μM	[130]
Prostate cancer			
EGCG	*in vivo*	1 mg 3×/week	[145]

Apigenin	*in vivo*	20 and 50 µg/ mouse	[146]
Genistein	*in vitro*	0.5–50 µM	[140]
Ellagic acid	*in vitro*	10–100 µM	[147]
Sesamin	*in vivo*	10 mg/kg	[119]
Resveratrol	*in vivo*	30 mg/kg	[148]
Resveratrol	*in vitro*	25–100 µM	[149]
Colorectal cancer			
Delphinidin	*in vitro*	30–240 µM	[150]
EGCG	*in vitro*	1–50 µM	[151]
Naringenin	*in vitro*	50–200 µM	[152]
Apigenin	*in vivo*	50 mg/kg	[153]
Luteolin	*in vitro*	20-100 µM	[154]
Kaempferol	*in vitro*	0–60 µM	[155]
Genistein	*in vivo*	20–80 mg/kg	[99]
Resveratrol	*in vitro*	25–150 µM	[156]
Cervical cancer			
Hesperetin	*in vitro*	650 µM	[82]
Genistein	*in vitro*	100 µM	[157]
Quercetin	*in vitro*	110.38 µM	[158]
Resveratrol	*in vitro*	150–250 µM	[159]
Liver cancer			
Xanthohumol	*in vitro*	5–40 µM	[160]
Daidzein	*in vitro*	200–600 µM	[161]
Sesamin	*in vitro*	25–125 µM	[118]
Ellagic acid	*in vivo*	30 mg/kg	[162]
Resveratrol	*in vitro*	25–100 µM	[156]
Resveratrol	*in vivo*	20 mg/kg	[163]
Gastric Cancer			
EGCG	*in vitro*	20–100 µM	[164]
Hesperetin	*in vivo*	20–40 mg/kg	[84]
Kaempferol	*in vivo*	20 mg/kg	[155]
Apigenin	*in vitro*	20 µg/mL	[165]
Gallic acid	*in vivo*	0.25% and 0.5% in water	[107]

Table 6: Mechanism of actions of Natural Plant derived Polyphenols.

Mechanism of Actions	Phenolic compounds	References
Antiangiogenesis and antimutagenic properties		
Inhibit cell proliferation, inhibit oncogene expression, induce tumor suppressor gene expression, and DNA binding prevention.	Favonoids (apigenin, daidzein, luteolin, kaempferol, myricetin, quercetin, hesperetin, EGCG, and genistein), Phenolic acids (chlorogenic acid and hydroxytyrosol), stilbenes (resveratrol), and lignans.	[166,167]
Induction of cell-cycle arrest and apoptosis		
Inhibit cell cycle at different phases: S/G_2, G_1, and S phases, direct or indirect effect on cell cycle arrest, involved in p53 and induce apoptosis.	Flavonoids (quercetin and EGCG), Phenolic acids (ferulic acid, caffeic acid, ellagic acid, and hydroxytyrosol), Stilbenes (resveratrol), and lignans (sesamin).	[166,168]
Inhibition of signal transduction pathways		
NF-κB and AP-1 signaling pathway, Nrf-KEAP1 (Kelch-like ECH-associated protein 1) complex signaling pathways, the Wnt or β-catenin signaling pathway, growth-factor receptor-medicated pathways, and MAPK signaling pathway.	Flavonoids (apigenin, genistein, quercetin, and EGCG), phenolic acids (caffeic acid and gingerol), lignans, coumarins, and stilbenes (resveratrol).	[168,169]
Antiviral, antibacterial, and antifungal effects		
Inhibit liver cancer and down-regulate HIV expression	Flavonoids, phenolic acids, stilbenes (resveratrol), and lignans.	[167]
Enzyme inhibition		
COX-2, iNOS, XO, signal transduction Enzymes such as PKC and PTK, phase I enzyme (block activation of carcinogens), and DNA methytransferases.	Flavonoids (apigenin, luteolin, quercetin, and EGCG), Phenolic acids (chlorogenic acid, caffeic acid, ellagic acid), stilbenes (resveratrol), and lignans.	[166,167]

Conclusion and Future Development

Cancer is a mind-boggling process which includes in the multiplication of cells, hindered cells passing, and worldly changes in the physiology of cells. Cancer remains a moment driving reason for death comprehensively. Malignancy happens because of dysfunction of numerous coding genes proteins including development factor receptors, hostile to apoptotic proteins, and so on. Lung, breast, colorectal, and stomach cancers are most prominent cancer among all. Pakistan has the most elevated breast cancer proportion among Asian nations, and most normal tumors in Pakistan are lung, breast, head and neck cancers, and lymphoma. Natural compounds are most supported for the treatment of carcinogen because of their security, proficiency, straightforwardness to accessibility, and hostile to malignant capacity. Phytochemicals shown a significant role against various malignancies, but among all, natural polyphenol compounds (flavonoids, phenolic acids, lignans, and stilbenes) represent a broad and assorted group in the anticipation and treatment of cancer. Natural polyphenols have their anticancer exercises through various pathways, including cancer prevention agent enzymatic movement, cell cycle arrest (S/G_2, G_1, S, and G_2 stages), by regulating the Nrf2 and NF-κB cells, inhibit the cell-proliferation, prompt apoptosis, MAPK flagging pathway, and so on. The anticancer impacts of polyphenol changed with the doses, cancer type, and cell lines.

The clinical trials are limited about the natural polyphenol compounds. In the future, more epidemiological investigations employing biomarkers of polyphenols are needed to assess the effect of dietary polyphenols on cancer hazard. It is recommended that the synthesis of well-targeted and well-designed phenolic compounds, can lead to the development of clinically beneficial drugs with efficiency and selectivity. In addition, various researches are required to investigate that which signals, and mechanisms are responsible for the regulation of apoptosis and cell cycle death after the treatment by using natural polyphenols.

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