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Review Based Book Chapter

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REVIEW BASED BOOK CHAPTER

EXPLORING THE BIOACTIVITY OF PHENOLIC COMPOUND

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Abstract

Polyphenols, a wide group of secondary metabolites found in plants and some animals too, have gained significant attention in recent years due to their outstanding bioactivity and potential therapeutic applications. This chapter will provide a brief overview of the bioactivity of polyphenols, highlighting their importance in the treatment of different disorders. Polyphenols exhibit strong anticancer properties, demonstrated through multiple in vitro and in vivo studies. Their potential to inhibit cancer growth, progression, metastasis, induction of apoptosis, and modulation of multiple signaling pathways involved in cancer make them effective candidates for the treatment of cancer. Furthermore, polyphenols have significant antibacterial action, by disrupting cell membranes and inhibiting the synthesis of different enzymes, making them valuable agents for overcoming bacterial drug resistance. Moreover, they also possess antiaging properties, attributed to their strong antioxidant potential. They assist in combating cellular damage and reducing the aging process by lowering oxidative stress and scavenging free radicals. In addition to all this, polyphenols exert antidiabetic effects by modulating the metabolism of glucose, increasing the sensitivity of insulin, and lowering oxidative stress, offering potential therapeutic benefits for being effective against diabetes mellitus. Polyphenols also show cardioprotective effects, with evidence describing their potential to improve cardiovascular health by lowering inflammation, blood pressure, and free radicals, and inhibiting aggregation of platelets. Furthermore, recent studies also highlight antiviral, anti-Alzheimer, antifungal, and antiparasitic activities. In conclusion, the abundance of literature overwhelmingly demonstrates the bioactivity of polyphenols against various diseases. Understanding the primary mechanisms behind the bioactivity of polyphenols holds great promise for developing innovative therapeutic interventions for different disease conditions.

Keywords: Bioactive Compounds, Polyphenols, Bioactivities, Signaling Pathways, In Vitor and In Vivo Studies

Phenolic compounds [PCs] include flavonoids, allied phenolic, chalcone, etc. are secondary metabolites, distributed cosmopolitan in plants. There are several ways to extract PCs from plants. PCs give color to plants, act as attractants in plants,

play a defensive role in plants, are a structural polymer of plants, have antioxidant activity in plants, signaling molecules, protect plants from pathogens, and have the well-studied role of phenolic in plant growth and metabolism. In fruits and vegetables, PCs contribute to color and sensory characteristics [1, 2].

PCs are found in cereals, fruits [cherries and citrus, etc.], vegetables, potatoes, cocoa, tomato, yam, kale, broccoli, Brussels sprouts, dark green leafy, bright-colored vegetables, legumes, and spices. Coffee, Green, and black tea contain numerous PCs [3]. The insect was used in traditional medicines. Certain flavones and flavonols are found in the following insects: Halkhill blue butterfly, Marbled white butterfly, Carolina locust, Common blue butterfly, Mulberry white caterpillar, Dark black chafer beetle, and Silkworm [4]. Likewise, certain phenolics can be extracted from animal urine [5], glands [6], hormones [7] of different animals like pigs, elephants, beavers, etc., and human sweat. Certain fungi from basidiomycetes [8], algae from [Rhodophyceae, Phaeophyceae, and Chlorophyceae] [9], and lichens contain PCs [10]. Due to the diverse availability of polyphenols traditionally they have been used for the treatment of multiple disorders like cancer, heart disease, or bacterial infections. Here below we will discuss the bioactive potential of polyphenols against different disorders.

1. Anticancer activity of Phenolic Compound

Cancer: a heterogeneous disease, with uncontrolled and impaired cell division, that can lead to abnormal growth, and even invade and metastasize to the whole body. Cancer is the principal cause of death worldwide. Internal causes of cancer include hypoxia, oxidative stress, genetic mutation, damaged DNA, abnormal hormonal levels, and loss of apoptotic function, etc. while external causes include pollution, smoking, radiation, ultraviolet, exposure to stress, viruses, chemicals, etc. The main characteristics of cancer cells are mutation, immune resistance, metastasis, angiogenesis, mitochondrial dysfunction, and metabolism alteration including excessive aerobic glycolysis, enzymatic activity, changes in lipids metabolism, changed pH, etc. [11].

There are various mechanisms to treat cancer like chemotherapy, radiotherapy, immunotherapy, targeted therapy, hormonal therapy, surgery, stem cell or bone marrow transplant, etc. The most common treatment for cancer is chemotherapy, which has comparatively less deleterious effects on the human body [12]. Natural compounds are always close to human nature and interest. Among the various

classes of natural compounds, phenolics have great importance. Most of the anticancer drugs almost 60-70% that are used nowadays a day is from natural sources [13]. PCs [PCs] exhibit diverse mechanisms of anticancer activity. PCs include several compounds that can arrest cell cycle at different phases, similarly, induce apoptosis in *in vitro* and *in vivo* models, and inhibit cell proliferation, metastasis, VEGF, and angiogenesis. Some well-known PCs can inhibit numerous cell signaling pathways, which can hinder cancer growth [11]. As shown in Figure 1.

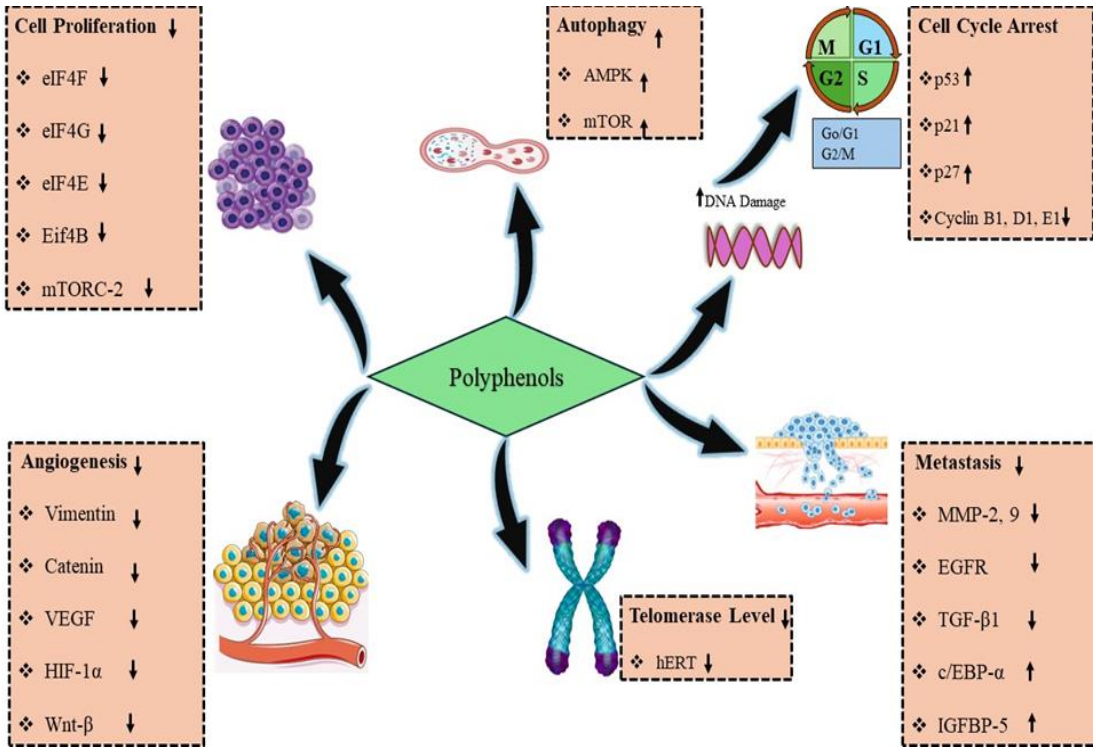


Figure 1 Anticancer mechanism of different PCs

A diverse class of phenolic includes many compounds that exhibit anticancer activity against many cancers in in vitro cell lines but to avoid complication here we will enlist some compounds that exhibit anticancer activity in both in vitro and in vivo models as described in Table 1 and Table 2.

Butein shows its anticancer effect against skin cancer [14], breast cancer [15], [16], colorectal cancer [17], hepatic cancer [18], lung cancer [19] and prostate cancer [20]. Garcinol acts against breast cancer [21, 22], prostate cancer [23], hepatic cancer [24], and cervical cancer [25]. Icariside II against osteosarcoma [26], cervical [27], breast [28], glioma [29], [30], esophageal [31], and glioma [32]. Gallic

acid against Lung Cancer [33], Osteosarcoma [34], Myricetin against Bladder Cancer [35], prostate cancer [36] Caffeic Acid against Lung Cancer [37], Curcumin against glioma [38] and glioblastoma [39], Quercetin against cervical cancer [40], Sinapic acid against pancreatic cancer [41], Kaempferol against Gastric cancer [42], cholangiocarcinoma [43], Osteosarcoma [44], Pterostilbene against Breast cancer [45], non-small-cell lung cancer [46], Esophageal Cancer [47], Colon Cancer [48], Resveratrol against bladder cancer [49, 50], colorectal cancer [51], lung cancer[52, 53], Gnetin C against prostate cancer [54], epigallocatechin gallate [EGCG] against colorectal [55], lung cancer [56], neural [57], oral [58] and breast cancer [59], Luteolin against liver cancer [31], [60], breast [61], Genistein against breast [62] and hepatic cancer [63], Tangeretin against gastric cancer [64], Daidzein against choriocarcinoma [65], Silymarin against gastric cancer [66] and Breast Cancer [67], Silibinin against liver [68], pancreatic [69], colorectal [70], cervical [71], prostate cancer [72, 73] and renal cancer [74], Apigenin against prostate [75, 76], colon [77], osteosarcoma [78], Naringenin against breast cancer [79], [80] and sarcoma [81]. Licoricidin against gastric [82] and colorectal adenocarcinoma [83], Echinatin against oesophageal cancer [84], Liquiritin against cervical cancer [85], Isorhapontigenin against prostate cancer [86], cardamonin against breast [87] and lung cancer [88], Phloretin against human triple negative breast cancer [89], cervical [90] liver [91] and lung [92], Xanthohumol against pancreatic [93], leukaemia [94], cholangiocarcinoma [95], breast [96], Flavokawain B against squamous carcinoma [78], breast [97, 98], Licochalcone A against glioma [99] and osteaosarcoma [100], Biochanin A against prostate [101], lung [102], glioblastoma [103], colorectal [104], breast [105], Hesperetin against oesophageal [106], renal [107] and breast cancer [108], Capsaicin against colon [109, 110] and bladder cancer [111], Allicin against Lymphoma [112], cholangiocarcinoma [113], colorectal [114] and bladder cancer [115] and formononetin against colon cancer [116], cervical [117], breast cancer [118], osteosarcoma [119], prostate [120], nasopharyngeal [121] and Human myeloma [122]. The enlisted compounds show evidence of anticancer activity against various cancers in vitro and in vivo models as given in table 1 and 2. These compounds put on display innumerable anticancer effects against cancer cell lines in vitro. Thus, fewer studied PCs in vivo models because of their low bioavailability [123].

Table 1 Molecular targets of polyphenols in different In-vitro studies

Sr. No	Phenolic Compound	Cancer Types	Cell Lines	Cellular targets		Dose	Reference
				Upregulate	Downregulate		
1	Gallic acid	Lung Cancer	A549	P53, Bax, p21, p27	Bcl-2, PI3K/Akt, Cyclin D1, E1	75 µM	[33]
2	Myricetin	Bladder Cancer	T24	G2/M phase arrest, caspase-3, p-p38, MAPK	Bcl-2, Cyclin B1, cyclin-dependent kinase cdc2, p-AKT, MMP-9	20–100 µM	[35]
		Prostate Cancer	PC3, DU145	E-cadherin, cl-caspase-3, cl-caspase-9	N-cadherin, vimentin, ERK1/2, AKT, Ki-67	0-100 µmol/L	[36]
3	Caffeic Acid	Lung Cancer	H1299	Caspase-3 and caspase-9, G1 cell cycle arrest, cl-PARP, Bax, Bid	Bcl-2, Bcl-xL	600 µM	[37]
4	Curcumin	Glioma	Tu-2449, Tu-9648	G2/M phase arrest	JAK 1,2/STAT3, c-Myc, MMP 9,snail, twist, Ki67	20 µmol/L	[38]
		Glioblastoma	U138MG	G2/M phase arrest	MMP, bcl-xl, PI3K/Akt, NF-KB	30 µM	[39]
5	Quercetin	Cervical Cancer	Caski, Hela, Siha	G2/M phase arrest, Bax, Bad, Cyto-c Apaf-1, cl-caspase-1	JAK2, mTOR, STAT5, Bcl-2, Cyclin-D1	0-100 µM	[40]
6	Sinapic acid	pancreatic Cancer	PANC-1, SW1990	E-cadherin	Cyclin E1, CDK2, Cyclin D1, CDK4, Vimentin, MMP-9, snail, AKT/Gsk-3β	2.5-10 mM	[41]
7	Kaempferol	Gastric Cancer	MKN28, SGC7901	G2/M phase arrest, Bax, cl-caspase-3, cl-caspase-9,cl- PARP	cyclin B1, Cdk1 and Cdc25C, Bcl-2, p-Akt, p-ERK and COX-2	0-120 µM	[42]
		Cholangiocarcinoma	HCCC9810 QBC939	Bax, Fas, cl-caspase 3, cl-caspase 8, cl-caspase 9, cl-PARP	Bcl-2, phosphorylated AKT, TIMP2, MMP2	30–150 µM	[43]
		Osteosarcoma	U-2 OS cells	Bax, cytochrome c, Apaf-1, caspase-9, caspase-3, caspase-7, AIF	Bcl-2	150 µM	[44]
8	Pterostilbene	Breast Cancer	MDA-MB-231 Hs578t	E-cadherin, miR-205	Snail, Slug, vimentin ZEB1, Src expression	2.5–10 µM	[45]
		Non-small-cell Lung Cancer	PC9, A549	ROS, Caspase 3, p-PERK, IRE1, ATF4, CHOP	GSH	20–60 µM	[46]
		Esophageal Cancer	EC109	Caspase 3 activity, ROS level, ERS-related molecules GRP78, ATF6, p-PERK, p-eIF2α, CHOP	Bcl-2	50–150 µM	[47]
		Colon Cancer	HT-29	-	b-catenin, cyclin D1, c-MYC,	50 µM	[48]
9	Resveratrol	Bladder Cancer	T24	G1 phase arrest, p38, Bax cl-caspase 3, cl-PARP	cyclin D1, cyclin-dependent kinase 4, phosphorylated Rb, phosphorylation of Akt, Bcl-2, Bcl-xL, p-Bad	50–200 µM	[49]

			TCC, EJ cells	S phase arrest	STAT3, survivin, cyclinD1, c-Myc and VEGF, Sirt1, p53	50–200 μM	[50]
		colorectal Cancer	LoVo	Vimentin, TGF-b1/Smads	TGF-b-induced EMT, E-cadherin	6.25–200 μM	[51]
		lung Cancer	SPC-A-1/CDDP cells	G0-G1 and S phase or at the G2/M phase arrest, caspase 3	Survivn	25–100 μM	[52]
10	Gnetin C	Prostate Cancer	DU145, PC3M	-	MTA1, Cyclin D1, Notch 2	25-50μM	[54]
11	Epigallocatechin Gallate	Colorectal Cancer	SW837 cells	-	p-IGF-1R, pERK, p-Akt proteins, VEGF, HIF-1, IGF-1, IGF-2, EGF	25 μg/ml	[55]
		Lung Cancer	H1299 cell	ROS	-	10–50 μM	[56]
		Neural Cancer	PC-12 cells	Bax, caspase-3, caspase-7	Bcl-2, APP	20–40 μM	[57]
		Oral Cancer	SCC-9 cells	-	MMP-2, uPA, FAK, Src, NF-κB, snail-1, MMP-9	5–20 μM	[58]
		Breast Cancer	MDA-MB-231 cell	-	Cyclin D, Cyclin E, CDK 4, CDK 1, PCNA	1–200 μg/ml	[58]
12	Luteolin	Liver Cancer	HepG2 cell	AMPK, ROS	NF-κB	0-100 μM	[31]
			HepG2, HAK1B	Fas/CD95, cl-caspase-3, PARP	STAT3, cyclin D1, survivin, Bcl-xL, CDK5	50 μmol/L	[60]
		Breast Cancer	MDA-MB-231, MCF-7	-	Notch-1, Hes-1, Hey, VEGF, Cyclin D1, MMP	100 μmol/L	[61]
13	Genistein	Breast Cancer	MCF-7/ERβ1 MDA-MB-231/ER	G_0/G_1 phase arrest, p-21, ERβ1	-	1,000 ppm	[62]
		Hepatocellular Carcinoma	HCC cell lines, Bel-7402 cells	G2/M phase arrest, caspases 3, caspases 9, Beclin1	PCNA, cl-PARP	60-80 μM	[63]
14	Tangeretin	Gastric Cancer	SGC7901	miR-410	Notch-1, Hey-1, Hes-1, Snail 1, Twist 1	0-100 μM	[64]
15	Daidzein	Choriocarcinoma	JAR, JEG-3	G1 phase arrest, p21	cyclin D1, c-myc, PCNA, p-ERK	0-100 μM	[65]
16	Silymarin	Gastric Cancer	AGS human gastric cancer cells	Bax, phos- phorylated [p]-JNK, p-p38, cl-poly-ADP ribose polymerase	Bcl-2, p-ERK1/2	0- 120 μg/ml	[66]
17	Silibinin	Liver Cancer	HCC HepG2 cells	caspase3, ROS, Bax	GSH, Notch1, RBP-Jk, Hes1 proteins, Bcl2, survivin, cyclin D1	50–200 μM	[68]

		Pancreatic Cancer	BxPC-3, PANC-1	G0/G1 phase arrest	Cyclin D1, CDK4/2	25-100 μM	[69]
		Colorectal Carcinoma	LoVo Cells	cl-poly–ADP ribose polymerase, cl-caspase–9, cl-caspase–3, G2-M-phase arrest, p21, p27	cyclins D1, cyclins D3, cyclins A, cyclins B1, Cdk 1, Cdk 2, Cdk 4, Cdk 6	50-200 μmol/L	[70]
		Cervical Cancer	SiHa, Hela cells	G2/M phase arrest, Drp1, ROS	CDK1, cyclin B1, cdc25C	0-450 μM	[71]
		Prostate Cancer	PC3 cells	β1, β3 [fibronectininduced integrins], FAK, Src, GTPases, ARP2, cortactin [actinremodeling], cl-PARP, cl- caspase 3, EMT, E-cadherin, βcatenin, α5, αV	survivin, Akt	50-200 μM	[72]
			PCa, LNCaP, 22Rv1 cells	-	NOX, lipid synthesis, HIF-1α, FASN, ACC levels, Ki-6, cyclin D1	0–200 μM	[73]
		Renal Cancer	769-P, 786-O, aCHn, OS-RC-2	cl-caspase–3, cl-PARP	Bcl 2, GLI1, p-mTOR	0-200 μM	[74]
18	Apigenin	Prostate Cancer	PC-3, 22Rv1	p21/waf1, bax protein, mRNA expression	HDAC1, HDAC3, bcl2	20–40 μM	[75]
			PC-3	caspase-9, BAD, cl-caspase–3, cl-caspase–9	p-Akt, glycogen synthase kinase-3, p-GSK3b, p-BAD Ser136	5–40 μM	[76]
		Colon Cancer	HT-29	Beclin-1, LC3-II, Bax	p-mTOR, p-PI3K, p-AKT, p62, Bcl-2	15–60 μM	[77]
		Osteosarcoma	U-2 OS cells	caspase-3, -8, -9, BAX, AIF, GADD153		75 μM	[78]
19	Naringenin	Breast Cancer	4T1- Luc2	-	NGE, TGF-β1, protein kinase C	100 μM	[79]
			MDA-MR-231	G0/G1 phase arrest, caspase-3, caspase -9	-	0–100 μM	[80]
		Sarcoma	Caco-2, HL60	-	NGE	100μl	[81]
20	Licoricidin	Gastric Cancer	MGC-803 cell	Bax, Cyt-C, Caspase 3, G0/G1 phase arrest	Bcl-2, cyclin D1, CDK4, MMP2, MMP9	1.5–200 μM	[82]
		Colorectal Adenocarcinoma	SW480	LC3-I, LC3-II	cyclin B1, CDK1, Bcl-2	0–20 μM	[83]
21	Echinatin	Esophageal Cancer	KYSE30 KYSE270	E-cadherin	p-AKT, p-mTOR, β-catenin, vimentin	20 μM	[84]
22	Liquiritin	Cervical Cancer	SiHa	Caspase-3, PARP, FADD,cl-Caspase 3, cl-Caspase 9, p21, p53	Bcl-2	40–80 μM	[85]
23	Isorhapontigenin	Prostate Cancer	PCa	Bim, p21, 27, Bax, cl-Caspase-3, cl-PARP1	p-Erk1/2, p-PI3 K, p-AKT, p-FOXO1, FOXO1, Sp1, Bcl-2, XIAP, Cyclin D1	0–100 μM	[86]

24	Icariside II or Baohuoside-I	Human Osteosarcoma Cells	MG-63, Saos-2	-	EGFR/mTOR activities	20-30 μM	[26]
		Cervical	Hela	ROS,Fas, TNF-R1, , Bax, P53, Bak, cyct C	p-AKT, cyclin D, CDK 6, CDK 4, cyclin A, cyclin E, CDK 2, caspase 8/3/9 BCL-2	10-30 μM	[27]
		Breast Cancer	MCF-10A HBL100, BT549, 4T1	-	Vimentin, MMP2	2-10 μM	[28]
		Hepatocellular Carcinoma	HuH-7, HepG2	BAX, caspase-3, caspase-8	Bcl-2, p-mTOR, p-S6K1	20-50 μM	[29]
			QGY7703	Bax, cleaved caspase-3	Bcl-2, P65, P50, IKβα	5-10 μM	[30]
		Esophageal Carcinoma	Eca109	-	Survivin, cyclin D1	50 μg/ml	[31]
25	Butein	Skin	B16F10	-	ERK, FAK, 4EBP, eIF4E, PI3K/Akt/mTOR/p70S6K signaling pathways, Akt and p-ERK1/2, p-mTOR, p70S6K, p-FAK, VEGF	1–10 μM	[14]
		Breast	MCF7-T47D	ERα degradation, Bax	ERα protein level, Cyclin D1, Ki67	0-20 μM	[15]
			MCF-7, MDA-MB-231, SKBr3, BT474	-	CXCR4,NF-kB,CXCL12	0-50 μM	[16]
		Colorectal	RKO, SW480, HCT116	cl- caspase-3, cl-PARP, p- CDC2, cyclin B1	phospho-CDC2 [Thr14], phospho-CDC2 [Tyr-15]	10–40 μM	[17]
		Hepatocellular	SMMC-7721, HepG2	cl- caspase-3, cl-PARP, Bax, P53	MDM2-mediated p53 ubiquitination	15-60 μM	[18]
		Lung Cancer	HBE cells, A549, PC-9, SPCA1 H1299 cells	G0/G1, G2/M phase arrest, Bax, caspase-8, caspase-9, ROS, NADPH, p-PERK eIF2α, ATF4, CHOP, IRE1α, XBP1	cdc25,Cylin-B1, cdc2 Bcl2, SOD2	5-60 μM	[19]
		Prostate	LNCaP, CWR22Rm1, PC3	Bax, caspases-3, -8, -9	cyclins D1, D2, E, cdks 2, 4,6, NF-κB, IκB kinase, IκBa,NF-κB DNAbinding activity,PI3K,p-Akt ,Bcl2	10–30 μM	[20]

26	Cardamonin	Breast Cancer	MDA-MB-231	OXPHOS, ROS	HIF-1a, mTOR/p70SK, Nrf2,	20 μM	[87]
		Lung Cancer	A549, H460	G2/M phase arrest, Bax caspases-3	Bcl-2, cyclin D1, CDK4, PI3K, Akt, mTOR	10–40 μM	[88]
27	Phloretin	Human Triple-negative Breast Cancer TNBC	MDA-MB-231	G0/G1, p27/Kip1, p21/Cip1, E-cadherin	cyclins E1, cyclins D1, p- FAK, p-Src	10–150 μM	[89]
		Human Cervical Cancer	SiHa	-	invasion, MMP-2, MMP-3, cathepsin S	60-100 μM	[90]
		Human Liver Cancer	HepG2	cl-caspases-3,cl-PARP, caspases-8,-9, Bax, Bad	Akt, Bcl-2, GLUT2	200 μM	[91]
		Lung Carcinoma	A549	cl-caspases-3, cl-caspases-9, cl-PARP, Bax, p53	Bcl-2, NF-κB, MMP-9	0-200 μM	[92]
28	Garcinol	Breast Cancer	MDA-MB-231, BT-549	E-cadherin, miR-200, let-7 family microRNAs [miRNAs]	ZEB-1, ZEB-2	25 μmol/L	[21]
			MDA-MB-231	-	MMP-9, STAT-3	25 μM	[22]
		Human Prostate Cancer	PC-3	Bax, caspase-3, -9, cl-PARP, p-GSK-3β,	Bcl-2, procaspases-3, -9, mTOR,	30 μM	[23]
		Hepatocellular	C3A, HepG2, HUH-7	caspase-3, cl-PARP	STAT3, cyclin D1, Bcl-2, Bcl-xL, Mcl-1, survivin, and VEGF	50 μM	[24]
		Human Cervical Cancer	Hela, SiHa	cl-caspase-3, cl-caspase-9, Bax, p21, p27, G0/G1 phase arrest, T-cadherin	Bcl-2, cyclin D1, CKD4, MMP-2, MMP-9, P13 K/AKT	25 μM	[25]
29	Xanthohumol	Pancreatic Cancer	BxPC-3 cells	-	NF-kB, VEGF, IL-8 mRNA	0-25 μmol/L	[93]
		Leukaemia	L1210 cells	Caspase 3/7, cl-PARP	AKT, NF-kB	5 μM	[94]
		Cholangiocarcinoma	XN, KKU-M214 CCA	Bax	STAT3, cyclin D1 and CDK4, Bcl-2	50 μM	[95]
		Breast Cancer	MCF-7, MDA-MB-231 cells	G0/G1 phase arrest, MIF, p21WAF1/CIP1, cl-caspase-3 cl-PARP, Bax	Notch 1, Hes1, c-Myc surviving, EGFR, CDK4 cyclin D, Bcl-2	5-20 μM	[96]
30	Flavokawain B	Human Squamous Carcinoma Cells	KB cells	caspase-9, -3 -8, cl- PARP, Bid, Bax, G2/M phase arrest, p21/WAF1, Wee1, p53	Bcl-2, cyclin A, cyclin B1, Cdc2, Cdc25C	5–20 μg/ml	[78]
		Breast Cancer	4T1	IL-2	-	13.5 μg/mL	[97]
			MCF-7 MDAMB231	G2/M phase arrest, p-p38 alpha, p-CREB, p-HSP27, p-JNK, p-AKT, p-ERK, p-HSP60, p-WNK1, p-c-Jun, p-p53	MMP9, VEGF, GLUT1 FOXM1, NF-KB, COX-2, VEGF, SNAIL, CXCR4	12-38 μM	[98]
31	Licochalcone A	Glioma Cell	U87	G0/G1, G2/M phases arrest	cyclin D1, CDK6, CDK4, cyclin E1,	20-30	[99]

					CDK2, cyclin A, cyclin B1, CDK1	μM	
		Osteosarcoma	HOS, U2OS	cl-caspase-3, cl-caspase-9, cl-PARP, Bax, p38MAPK	Bcl-2, Mcl-1	20-60 μM	[100]
32	Biochanin A	Prostate	LNCaP cell	SH3GL1, SH3 domain GRB2-like 1	Cadherin 2, prefoldin 5, SLC25A3, LOC51323, NDUFA5, NADH	0–50 μg/mL	[101]
		Lung	A549, 95D	S phase arrest, Bax, cl-Caspase-3, P21	cyclin A, CDK2, Bcl-2	50– 400 μmol/L	[102]
		Glioblastoma	U251 cell	ROS, Bax Cyt-C, Pro-caspase 3	Bcl-2, MFN1, MFN2 AKT, mTOR, HIF-1α Glut-1, HK2, and LDHA	0–100 μM/L	[103]
		Colorectal	HCT116, SW620	E- Cadherin	PD-L1, ZEB1, N- Cadherin	20–100 μM	[104]
		Breast	MDA-MB-231, MCF-7 cells	p-p53, p-p38, p-ASK1 proteins	TRAF2	30–70 μM	[105]
33	Hesperetin	Esophageal Cancer	Eca109 cells	cl-caspase-9, cl-caspase-3, Apaf-1, Bcl-2-associated X protein [Bax], SuFu	Cyt C, AIF, Bcl-2, survivin	100–200 μM	[106]
		Renal Cancer	HK2	Nrf2 signaling, SIRT6, NQO1, HO-1	SCr, BUN, MDA, MPO, GSH, SOD, NOX4	2.5–10 μM	[107]
		Breast Cancer	MCF-7	p57Kip2 expression	Aromatase enzyme Cyclin D1,CDK4,Bcl-xL, pS2	500–5000 ppm	[108]
34	Capsaicin	Colon Carcinoma	HCT116	Vimentin, N-Cadherin, p- ERK1/2	epithelial markers, E-Cadherin, ZO-1	1–10 μM	[109]
			colo 205 cells	ROS, Fas, cytochrome c, Bax	Bcl-2	150–300 μM	[110]
		Bladder Cancer	T24 cells, Bca 5637	E-Cadherin, beta-catenin, G0/G1 phase arrest	N-Cadherin, CDK2, CDK4, CDK6, cyclin D1, PI3K/Akt/GSK3β signaling pathway p-AKT/GSK3β were all strongly downregulated	50–300 μM	[111]
35	Formononetin	Colon Carcinoma	RKO	Bax	Bcl-2, p-ERK	5–40 μM	[116]
		Human Cervical	HeLa cells	Bax, cl-caspase-3	Bcl-2, p-AKT	0-10 μmol/L	[117]
		Breast Cancer	MDA-MB231-luc, 4T1	TIMP-1, TIMP-2	PI3K/AKT	2.5-180 μM	[118]
		Osteosarcoma	U2OS	-	miR-375, Ki-67, p-PI3KCA, p-AKT	50–100	[119]

						μM	
		Human Prostate Cancer	PC-3, DU145	-	CDK4, cyclin D1, mRNA expressions, CDK4, AKT	10–100 μM	[120]
		Nasopharyngeal	CNE1, CNE2	Bax, caspase-3 mRNA, p-JNK1/2, p-p38	p-AKT, Bcl-2	5–40 μM	[121]
		Human Myeloma	U266, RPMI 8226	caspase-3, cl-PARP	p-STAT3, p-STAT5, cyclin D1, cyclin B1	50–100 μM	[122]
36	Allicin	Lymphoma	L5178Y	caspase-3	-	72 μg/mL	[112]
		Cholangiocarcinoma	HuCCT-1 QBC939	Caspase 3, Caspase 9, Bax, E-Cadherin	Bcl-2, MMP-2, MMP-9, vimentin	10–40 μM	[113]
		Colorectal Cancer	HCT116	-	pSTAT3, MCL-1, Bcl-2, Bcl-xL	25 μM	[102]
		Bladder Cancer	MBT-2	-	-	0.1–2.5 mg/mL	[115]

Table 2 Molecular targets of polyphenols in different In-vivo studies

Sr. No	Phenolic Compound	Cancer Types	In-vivo	Dose	Mechanism of action	Reference
1	Gallic acid	Lung Cancer	A549 Xenograft	50 mg/kg	Inhibited tumor growth by downregulating expressions of PCNA and p-Akt, upregulating cl-caspase-3	[33]
		Osteosarcoma	MNNG/HOS xenograft	-	Decrease xenograft tumor growth, down-regulation of PCNA and CD31 expression and up-regulation of apoptosis in MNNG/HOS tumor in dose-dependent manner	[34]
2	Myricetin	Bladder Cancer	T24 Xenograft	5 mg/kg	Antitumor effects on bladder cancer xenograft model	[35]
		Prostate Cancer	PC3 subcutaneous xenograft nude mice model	25 mg/kg	Suppressed the growth of xenograft tumor, cl-caspase 3, E-cadherin upregulated , N-cadherin and vimentin downregulated	[36]
3	Caffeic acid	Lung Cancer	H1299 xenografts	50 mg/kg	Cell proliferation was reduced by increasing the expression of p-JNK and p-ERK	[37]
4	Curcumin	Glioma	Glioma xenografts	20 μmol/L	Decrease tumor growth by downregulation of JAKs and upstream of STAT3	[38]
		Glioblastoma	C6-implanted Wistar rats	50 mg/kg/day	Reduced tumor size	[39]
5	Quercetin	Cervical Cancer	human cervical cancer Caski tumor xenograft models	-	Enhanced apoptosis, Reduced cancer cells proliferation, Reduced xenograft growth and development	[40]

6	Sinapic acid	Pancreatic Cancer	SW1990 xenografts	20 mg/kg	Inhibiting tumor migration and invasion, delay the progression of pancreatic cancer	[41]
7	Kaempferol	Gastric Cancer	SGC7901 cell-derived xenograft tumors	20 mg/kg	Suppressed the growth of the tumor xenografts	[42]
		Cholangiocarcinoma	QBC939 cell-derived xenograft tumors	20 mg/kg/day	Significantly inhibit tumor growth	[43]
		Osteosarcoma	BALB/c[nu/nu] mice	50 mg/kg	Reduce tumor size	[44]
8	Pterostilbene	Breast Cancer	MDA-MB-231-bearing NOD/SCID mice	10 mg/kg body weight, 3 times a week	Suppressed tumor growth and metastasis, reducing Src/Fak signalling	[45]
		Non-small-cell Lung Cancer	PC9 xenografs	50 mg/kg	Upregulation of Bax, Caspase 3 and p53 levels, and downregulation of Bcl2 protein	[46]
		Esophageal Cancer	EC109 xenografts in athymic nude mice	100-200 mg/kg	Inhibited tumor growth	[47]
		Colon Cancer	F344 male rats	40 p.p.m	Reduction in PCNA marker, downregulates the expression of b-catenin and cyclin D1, phosphorylated p65 [Ser 276], iNOS, COX-2 and inhibit inflammatory cytokines TNF-a, IL-1b and IL-4	[48]
9	Resveratrol	Bladder Cancer	bladder cancer xenograft model	20mg/kg	Reduce tumor growth, expression level of VEGF and FGF-2	[49]
			BALB/c-nude mice orthotopic xenograft models	50–200 μM	Growth suppression, distinctive apoptosis and STAT3 inactivation	[50]
		Colorectal Cancer	LoVo-pLV4-GFP cell	50-150 mg/kg	Inhibited the lung metastases, hepatic metastases in mice orthotopic transplantation	[51]
		Lung Cancer	SPC-A-1/CDDP cells	1-3 g/kg/ day	Inhibited the proliferation of SPC-A-1/CDDP cells, induced apoptosis	[52]
			A549 human lung cancer xenografts in nude mice	60 mg/kg	Inhibit tumor growth	[117]
10	Gnetin C	Prostate Cancer	PC3M-Luc Xenografts	50 mg/kg	Antitumor effect, reduce cell proliferation	[54]
11	Epigallocatechin Gallate	Colorectal Cancer	SW837 xenografts in nude mice	-	The expression levels of VEGFR-2 and p-VEGFR-2 proteins were decreased, inhibited the phosphorylation of ERK and Akt proteins	[55]
		Lung Cancer	H1299 xenograft	30 mg/kg/d	Inhibit xenograft tumor growth by inducing oxidative stress and cell apoptosis	[56]
		Neural Cancer	PC-12 rat pheochromocytomacells [s.c.] into male BALB/cnude mice	15 mg/kg	Inhibit xenograft tumor growth and induce tumor cell apoptosis via epigenetic regulation of APP	[57]
		Oral Cancer	SCC-9 oral cancer cells	10-20 mg/day/kg	Inhibit xenograft tumor growth	[58]

			[s.c.]into the right front axilla ofBALB/c nude mice			
		Breast Cancer	human tumor xenograft in nude mice	1-3 mg	Decrease proliferation and increase apoptosis	[58]
12	Luteolin	Liver Cancer	HepG2 Tumor xenograft model	10 μg/kg every 2 days for 3 weeks	Inhibit tumor growth significantly,	[31]
			HAK-1B hepatoma xenografted tumors	50 μmol/L	Inhibited tumor growth	[60]
		Breast Cancer	xenografted tumors	20-40 mg/kg/d	Inhibit tumor growth significantly,	[61]
13	Genistein	Breast Cancer	xenografted tumors	1,000 ppm	Inhibited tumor growth	[62]
		Hepatocellular Carcinoma	xenograft mouse model	40- 80mg kg^{-1}	Increase apoptosis	[63]
14	Tangeretin	Gastric Cancer	SGC7901tumor xenograft	30 mg/kg	Reduction in tumor	[64]
15	Daidzein	Choriocarcinoma	JEG-3 xenograft	10-20 mg/kg	Anti-proliferation function as xenografts growth was inhibited and expressions of c-myc, PCNA and p-ERK were suppressed	[65]
16	Silymarin	Gastric Cancer	Xenograft tumor model BALB/c nude mice	100 mg/kg	AGS tumor volume and increased apoptosis	[66]
		Breast Cancer	Male BALB/c nude mice	25-50 mg/kg	MCF–7 tumor growth was inhibited without organ toxicity. In MCF–7 tumors, silymarin induced apoptosis and decreased p–ERK1/2 levels	[67]
17	Silibinin	Liver Cancer	HepG2 xenografts in athymic nude mice	200-400 mg/kg	Inhibit tumor growth, downregulation of NICD, cyclin D1, surviving, Bax upregulated	[68]
		Pancreatic Cancer	BxPC-3, PANC-1 xenograft model	0.5% w/w	Increase apoptosis	[69]
		Colorectal Carcinoma	LoVo xenograft athymic nude mice	100-200 mg/kg/d for 5 days/wk	Inhibited the growth of LoVo xenograft, inhibits proliferation, increases apoptosis, increase in p27 levels, decrease in retinoblastoma phosphorylation	[70]
		Cervical Cancer	xenograft mouse mode	150-300 mg/kg	Inhibit tumor growth	[71]
		Prostate Cancer	Athymic [nu/nu] male nude mice injected with PC3	200 mg/kg	Inhibits invasiveness of cells	[72]
			Athymic [nu/nu] male nude mice with 22Rv1 cells	200 mg/kg	Tumor growth inhibition	[73]
		Renal Cancer	Male BaLB/c [nu/nu] mice injected with 786-O cells	200 mg/kg	Reduced RCC tumor growth	[74]
18	Apigenin	Prostate Cancer	PC-3 xenografts in athymic	20-50	Reduction in tumor growth, HDAC, HDAC1, HDAC3 protein	[75]

			nude mice	μg/mouse/day	expression, increase p21/waf1 expression	
			PC-3 xenografts in athymic nude mice	20-50 μg/mouse/day	Inhibited the growth of tumor xenograft	[76]
		Colon Cancer	Xenografts model	35 mg/kg	Supress tumor growth	[77]
		Osteosarcoma	U-2 OS xenograft tumor	2 mg/kg	Supress tumor growth	[78]
19	Naringenin	Breast Cancer	4T1- Luc2 Balb/c mice	200 mg/kg	Inhibit tumor growth	[79]
			MDA-MR-231 xenograft	2.5-10 mg/kg	Inhibit tumor growth	[80]
		Sarcoma	Sarcoma S-180-implanted mice	30-300 mg/kg	Supress tumor growth	[81]
20	Licoricidin	Gastric Cancer	MGC-803 cell xenografted	20 mg/kg	Block tumor growth, upregulate Bax, downregulate Bcl-2, block ICMT/Ras signaling	[82]
		Colorectal Adenocarcinoma	SW480 Male Balb/c-nu/nu nude mice	5-20 mg/kg	Inhibit tumor growth	[83]
21	Echinatin	Esophageal Cancer	KYSE270-derived tumor xenografts	20-50 mg/kg	Inhibit tumor growth, decreased expression levels of p-AKT and p-mTOR	[84]
22	Liquiritin	Cervical Cancer	Male nude mice	10-30 mg/kg	Inhibit tumor growth	[85]
23	Isorhapontigenin	Prostate Cancer	xenotransplanted tumor in nude mice	50 mg/kg	Inhibit tumor growth, induce apoptosis, AR, p-AKT, p-Erk1/2, p-EGFR, p-FOXO1, CyclinD1, XIAP down-regulated, whereas c-Caspase-3 and c-PARP-1 were upregulated	[86]
24	Icariside II or Baohuoside-I	Human Osteosarcoma Cells	Male ICR mice	10-30 mg/kg·d	Inhibition of cell proliferation via the EGFR/ mTOR signaling pathway and downregulation of Ki-67 expression	[26]
		Cervical	Female BALB/c nude	25 mg/kg·d	Reduction of tumor volume and weight by inducing cell apoptosis and downregulation of MMP2/9	[27]
		Breast Cancer	mouse breast cancer xenografts	10-20 mg/kg/d	Supress tumor by modulating the TAMs/CXCL1 pathway	[28]
		Hepatocellular Carcinoma	xenografts in nude mice	25 mg/kg	Expression of MMP-2, MMP-9, p-mTOR and Bcl-2 protein significantly decreased while the expression of Bax protein increased	[29]
			QGY7703 tumor bearing nude mice	5-10 mM	Suppresses the Proliferation	[30]
		Esophageal Carcinoma	xenograft tumor model	25 mg/kg	Inhibits in vivo tumor growth, downregulation of β-catenin, cyclin D1, surviving	[31]
		Glioma	glioma in nude mice	35 mg/kg	Increased the expression of p-AMPKα1 and decreased the expression of p-mTOR	[299]
25	Butein	Skin	C57BL/6 mouse injected with	1-10 mg/kg	Reduction in lung metastases	[14]

			B16F10 cells			
		Breast Cancer	Nude balb/c mice xenografted with MCF-7 cells	10 mg/kg/2 day	Decreased tumor volumes and weight	[15]
			Nude [nu/nu] mice xenografted MDAMB-231 cells	10 µg/mL	Suppression of cancer growth	[16]
		Colorectal	BALB/cAnN.Cg-Foxn1nu/ CrlNarl mice with HCT116	40 mg/kg	Decreased tumor growth ability	[17]
		Hepatocellular	Balb/c nude mice xenografted with HepG2 Cells		Decreased tumor Growth	[18]
		Lung Cancer	Nude mice xenografted with PC-9 cells	10 mg/kg	Decreased tumor Growth	[19]
		Prostate	Athymic nude mice implanted with AR-positive CWR22Rm1 human PCa cells	-	Inhibition of tumor growth, downregulate Ki67,VEGF, CD31 in tumors	[20]
26	Cardamonin	Breast Cancer	MDA-MB-231 xenograft model	3 mg/kg	Inhibitory effects on tumor angiogenesis, increased cl-caspase3, Bax while decrease Bcl-2	[87]
		Lung Cancer	BALB/c nude mice	5 mg/kg	Tumour volume and weight were significantly reduced, Ki-67, p-Akt and p-mTOR expression was lower,	[88]
27	Phloretin	Human Triple-negative Breast Cancer TNBC	BALB/c nude mice MDA-MB-231 tumor xenografts.	10-50 mg/kg	Decreased tumor Growth, decrease in N-cadherin, vimentin, increase in p53, p21, E-cadherin	[89]
		Human Cervical Cancer	tumor xenograft model	10-20 mg/kg	Suppress metastasis and tumor growth in SiHa cells	[90]
		Human Liver Cancer	SCID mice bearing HepG2 tumor xenografts	10 mg/kg	Induce apoptosis	[91]
		Lung Carcinoma	A549 lung tumor xenografts	20 mg/kg	Inhibitory effect on lung carcinoma xenograft growth in mice	[92]
28	Garcinol	Breast Cancer	xenograft mouse model	5 mg/d	Inhibit NF-kB, miRNAs, vimentin, and nuclear b-catenin	[21]
			MDA-MB-231 breast cancer mouse xenograft model	5 mg/d	Inhibition of STAT-3 signaling	[22]

		Human Prostate Cancer	PC-3 xenograft prostate cancer mice	50 mg/kg	The tumor size was reduced more than 80 percent	[23]
		Human Hepatocellular Carcinoma	HCC xenograft tumors in athymic nu/nu mice	2 mg/kg	Inhibition of STAT3 activation, Bcl-2 downregulated and caspase-3 increased	[24]
		Human Cervical Cancer	mouse xenograft model	2 mg/kg	p-AKT and P13 K were significantly downregulated	[25]
29	Xanthohumol	Pancreatic Cancer	xenograft model of pancreatic cancer BxPC-3 cells	10 mg/k	Inhibited tumor growth, downregulated the expression of Ki-67 and CD31, decreased the activation of NF-kB p65 and the expression of VEGF and IL-8 in tumor tissues	[93]
		Leukaemia	murine L1210 leukemia	50 µg/ day, 5 days/week	Inhibitory effect on tumor growth	[94]
		Cholangiocarcinoma	XN, KKU-M214 CCA mouse model	50 µM	Inhibits STAT3 activation and tumor cell proliferation, but induces apoptosis in the CCA mouse model	[95]
		Breast Cancer	4T1 breast tumor mouse model BALB/c mice	100-200 mg/kg	Suppression of tumor growth, Notch1 and Ki-67. Survivin was downregulated and cleaved caspase-3 was upregulated	[96]
30	Flavokawain B	Human Squamous Carcinoma Cells	KB cell-derived tumor xenografts in nude mice	0.75 mg/kg every 2 days	Inhibitory effect on tumor growth	[78]
		Breast Cancer	Flavokawain B-treated mice	50 mg/kg	NF-κB, inducible nitric oxide synthase, intercellular adhesion molecule 1, and C-MYC declined in the FKB-treated mice, reduce tumor	[97]
			ex-vivo rat aortic	-	Potential inhibitor in angiogenesis	[98]
31	Licochalcone A	Glioma Cell	orthotopic xenograft tumor models of NU/NU mice	10 mg kg−1; once every 2 days	Reduced tumor growth	[99]
		Osteosarcoma	143B xenograft mice	10 mg/kg	[Bax, cleaved-caspase-9 and cleaved-PARP upregulate] downregulation Bcl-2, Reduction in tumor	[100]
32	Biochanin A	Prostate	NCaP xenografts	400 µg	Significantly reduced tumor size	[101]
		Lung	Xenografts model	15-72 mg/kg	Increase Apoptosis	[102]
		Glioblastoma	BALB/c nude mice	50 mg/kg	Increase Apoptosis	[103]
		Colorectal	CRC cell mouse mode	50 mg/kg daily	Downregulate Tumor progression and Immune escape	[104]
		Breast	Murine xenograft mode	5 mg/kg	Downregulate migration and invasion	[105]
33	Hesperetin	Esophageal Cancer	xenograft tumor model	30-90 mg/kg	Significantly reduced tumor size	[106]
		Renal Cancer	AKI mice	50 mg/kg	Increase Apoptosis, reduced Nephrotoxicity	[107]
		Breast Cancer	Female athymic mice	500–5000 ppm	Decrease Cell proliferation	[108]
34	Capsaicin	Colon Carcinoma	female BALB/c nude mice	-	Reduced tumor	[109]

			Colon 205 Tumor Xenografts	1-3 mg/kg	Inhibit tumor growth	[110]
		Bladder Cancer	Tumor Xenografts	20 mg/kg	Inhibit tumor growth, strongly upregulation of proteins involved in ROS metabolism	[111]
35	Formononetin	Colon Carcinoma	RKO xenograft	5-20 mg/kg	Reduction of tumor weight and volume, downregulation of TNF-α and NF-κB expressions	[116]
		Cervical Cancer	HeLa cells cervical tumor xenografts	20-40 mg/kg	Inhibit tumor growth	[117]
		Breast Cancer	MDA-MB231-luc breast cancer xenograft	10-20 mg/kg/day	Inhibition of metastasis	[118]
		Osteosarcoma	U2OS xenograft	25-100 mg/kg/day	Reduction of tumor mass Downregulation of miR-375 Reduced expressions of ERα, p-PI3KCA, p-AKT proteins	[119]
		Human Prostate Cancer	PC-3 xenograft	15-60 mg/kg/day	Reduction of tumor growth and tumor weight	[120]
		Human Nasopharyngeal Carcinoma	CNE1 xenograft	10-20 mg/kg	Reduction of tumor volume	[121]
		Human Multiple Myeloma	myeloma xenograft	20-40 mg/kg	Inhibition of tumor growth, downregulation of p-STAT3/5 expression levels, downregulation of Ki-67 expression, inhibit angiogenesis	[93]
36	Allicin	Lymphoma	BALB/c mice inoculated with L5178Y	20 mg/kg	Reduction of tumor volume	[112]
		Cholangiocarcinoma	Nude athymic mice bearing cholangiocarcinoma xenografts	10 – 20 mg/kg	Reduction of tumor volume, upregulate p-STAT3 levels and downregulate cl-caspase 9, Vimentin	[113]
		Colorectal Cancer	C57BL/6 mice treated to develop colorectal cancer	0.24 mg/day	Number of tumors and Tumor size decrease	[102]
		Bladder Cancer	CH3 mice bearing MBT-2 xenograft	12.5–25 μg	Tumor size decrease	[115]

1.1. Apoptotic effects of PCs

Apoptosis induction is the most important tool to combat cancer. Apoptosis means predetermine cell death. Apoptosis plays a positive role in embryonic development and adulthood as well as to counteract cancer. Cancer cells change the level of pro-apoptotic or anti-apoptotic protein through post-translational modification, which can lead to tumorigenesis. Apoptosis is the self-destruction of cells. The mechanism of apoptosis caused by different polyphenols is extrinsic, intrinsic, or perforin/granzyme pathway as shown in Figure 2 [124].

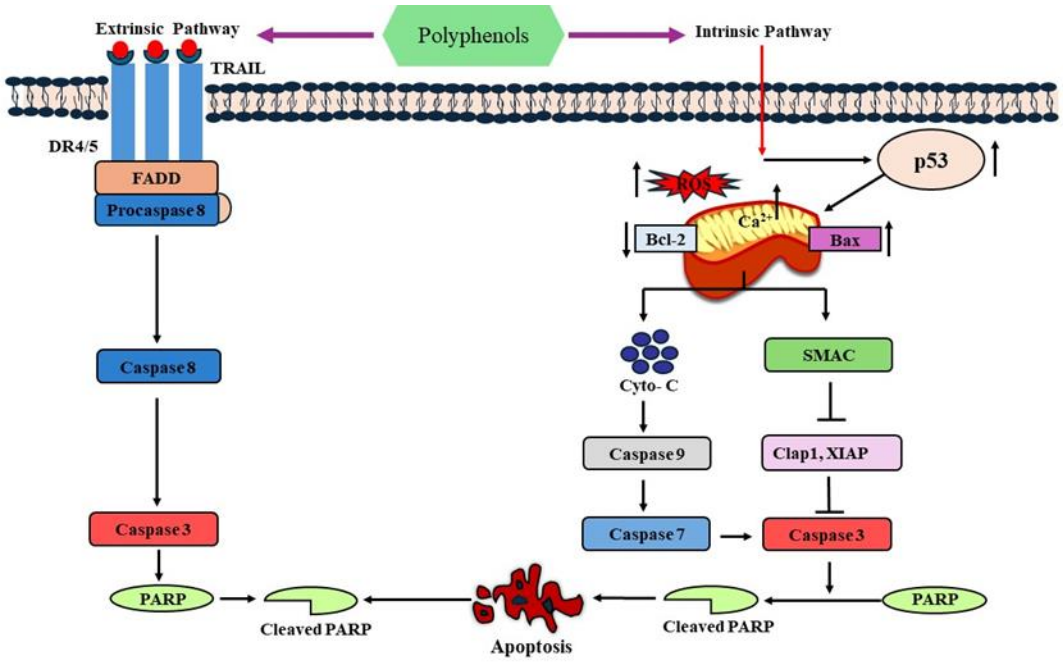


Figure 2 Apoptotic effects of different polyphenols

Butein flavonoid and chalcone induce apoptosis in various cancer cell lines and target the Bcl-2 family protein, Bax, and various caspases. Butein shows a strong anticancer effect against in vitro cancer cell lines e.g. skin, oral squamous cell carcinoma, head and neck, leukemia, osteosarcoma, multiple myeloma, breast, hepatic, pancreatic, lung, colorectal, bladder, kidney, prostate, cervical, and ovarian cancer. Butein induces apoptosis in osteosarcoma and prostate cancer by activating Bax and downregulating Bcl-2, and caspase-8 activates cytochrome c. Another target of Butein was STAT3, downregulation of STAT3 causes apoptosis through Bcl-2, Bcl-xL, cyclin D1, cyclin D2, cyclin E, CDK 2, CDK 4, CDK 6

downregulation. Butein also targets NF-κB in prostate cancer which leads to a decrease in the expression of anti-apoptotic proteins like Bcl-2, Bcl-xL and inhibits apoptosis 2 [IAP2], c-Myc, COX-2, and MMP-9 [125]. Kaempferol is flavonol and phytoestrogen, which induces apoptosis in various cell lines like MKN28, SGC7901, HCCC9810, QBC939, U-2 OS cells.

Kaempferol decreased the level of anti-apoptotic protein Bcl-2, pAKT, PLK-1 [polo-like kinase 1], pMEK ½, CDK1 and cyclins A, B, D1 and cyclin E, while upregulated the expression of p21, p53, Bax, cl-caspase-9, -7 PARP and p-ATM [126]. Apigenin a flavone, its anticancer activity is recorded against prostate, osteosarcoma, and colon cancer. In PC-3 cell line, apigenin upregulated Bax and downregulated the expression of Bcl-2 and Bcl-xl by cytochrome c release from mitochondria and activates signaling cascade. In PC-3 cell line, apigenin increases the expression of caspase-9, BAD, cl-caspase–3 and cl-caspase–9. In U-2 OS cells the activity of caspase-3, -8, -9 was upregulated. Apigenin increases to p53 level in ACHN cell line and Caki-1 RCC cell lines. In T24, bladder cancer cell line, PI3K/Akt pathway inactivated by apigenin which activates the intrinsic apoptotic pathway [127]. Another broadly studied polyphenol is EGCG [epigallocatechin-3-gallate], a potential inducer of apoptosis via mitochondria. In PC-12 neural cell lines, 20-40 μM concentration of EGCG increases the Bax and decrease anti-apoptotic protein Bcl-2. EGCG induces extrinsic apoptosis via Fas, DR5, and caspase-8 activation in MIA-PA-Ca-2 cell lines. Similarly, 1-3 mg of EGCG increases apoptosis in in-vivo human breast tumor xenograft in nude mice [128]. Resveratrol a polyphenol inhibits PI3K/AKT pathway in colon cancer in dose dependent manner. 20-50 μM of resveratrol inhibit PI3K/AKT/mTOR and PI3K/AKT/FOXO in prostate PC-3 and LNCaP cancer cell line [129]. Formononetin is an isoflavone, which induces apoptosis in multiple cancer cells like multiple myeloma, nasopharyngeal carcinoma, ovarian cancer, osteosarcoma, non-small cell lung carcinoma, and prostate cancer. In ovarian cancer, exposure to formononetin increases the expression of cl-caspase-3 and -9 in a dose-dependent manner. Similarly, the expression of caspase-3 and cl-PARP was upregulated in multiple myeloma and nasopharyngeal carcinoma. It was reported in the literature that formononetin modulates the expression of pro-apoptotic and anti-apoptotic proteins and induces changes in Bax/Bcl-2 ratio in colon and prostate cancer [130]. Capsaicin is a flavonoid, which actively induces apoptosis in pancreatic, colonic, prostatic, liver, esophageal, bladder, skin, leukemia, and lung

cancer. Mori et al. explain that capsaicin provoked apoptosis in a p53-independent manner in both in-vitro and in-vivo prostatic cancer xenograft models. A relative study was carried out on urothelial cancer cells where capsaicin upregulated the expression of p53 and phosphorylated at Ser-15, Ser-20, Ser-392 result in apoptosis induction [131].

Both Hesperidin and Hesperetin, modulate extrinsic apoptotic pathway by upregulating death receptors like Fas and FADD, initiated by oxidative stress. Besides this, hesperidin increased the expression of DR3 and TRADD receptors which in turn activates caspase-8. In reported literature, it has been shown that both hesperetin and hesperidin activate caspase-8. Both these compounds are also involved in the intrinsic apoptotic pathway. Hesperetin and hesperidin induced apoptosis in a few cell lines, hesperidin increased Bid, Bax, Bak and decreased Bcl-xl, Bcl-2, and Mcl-1 while hesperetin upregulated Bax and Bad and suppressed Bcl-2, Mcl-1 and surviving [132]. Biochanin A an isoflavone, arrests cell proliferation of head and neck cancer through NF-κB. Moreover, biochanin A induces apoptosis in lung and prostate cancer by inhibiting the NF-κB pathway. In FaDu cancerous cells, it downregulated MMP-2/-9 [matrix metalloproteinase-2/-9], leading to a reduction in p38MAPK and Akt pathways [133]. Another study by Tang et al. was found that it provoked apoptosis in DU145 and PC-3 cell lines by activating several caspases. It activates Bim, Bax, and Puma whereas deactivates the expression of XIAP and survivin [134].

1.2. Cell Cycle Arrest Induced by PCs

Cell cycle arrest is a crucial process of cell biology and helps in preventing cancer progression. Cell cycle arrest is involved in the homeostasis process of organisms and normal growth. Irregular or uncontrolled cell cycle leads to cancer progression. The cell undergoes normal division by passing through interphase [G1, S, and G2] and M phase. Interphase is a state of great metabolic activity while the M phase is the division phase which includes prophase, metaphase, anaphase, and telophase. If the cell faces any toxic or stress stimuli or DNA damage, the cell undergoes a quiescence stage in which reversible growth arrest and low metabolism take place. After repairing and tolerating damage, a cell may re-enter the state of division. In senescence, the cell completely loses the ability to divide. Cellular stress, ionizing radiation, chromatin damage, DNA damage, endogenic replication stress, oxidative

stress, and certain external factors lead to quiescence and senescence. The cell cycle is controlled by either cyclins or CDKs [cyclin-dependent kinase] [135]. CDKs play a crucial role in phosphorylation of Retinoblastoma protein [Rb], p107, and p130. CDKs are a family of serine/threonine that, when activated form complexes with cyclins. The CDKs/cyclins complex leads to cell cycle progression. Cyclin D-CDK4/6 and Cyclin E-CDK2 lead to the activation of Rb, p107, and p130 which in turn activates E2F transcription factor which helps in DNA synthesis. This enables the cell to jump from the G1 phase to the S phase. Different types of CDKs like CDK 2, 4, and 6 while cyclins include A2, B1, B2, D1, D2, D3, E1, E2 and G1 drive cell cycles. CDKIs are inhibitors of CDKs that help to prevent cell cycle progression. There are two main classes of CDKIs: INK4 and Cip/Kip. INK4 includes p16INK4a and p15INK4b inhibits CDK 4 and 6 while Cip/Kip contains p21Cip1, p27Kip1, and p57Kip2, these proteins inhibit CDKs activity [in response to stress activity], preventing aberrant cell division and maintain genome stability. Overexpression or deregulation of CDKIs induces abnormalities in cells [135].

Resveratrol is a polyphenol, which arrests the cell cycle in various cancer cell lines like T24, and TCC [49], [50]. It arrests the cell cycle in the G1-S phase arrest in bladder cancer, G0-G1, and S phase, or at the G2/M phase cell cycle arrest in lung cancer [52]. It downregulates CDK4 and cyclin D1. Kaempferol arrests the cell cycle at G2-M phase in gastric cancer MKN28 and SGC7901 cell lines in by downregulating cyclin B1, Cdk1, and Cdc25C [42]. Butein inhibits the cell cycle in lung cancer at Go/G1 and G2/M phase arrest by a decrease in expression of cdc25, Cylin-B1, and cdc2 [19]. Formononetin induces cell cycle arrest in several cancers like multiple myeloma, prostate, lung, breast, and ovarian cancer cells. In human myeloma cell line U266 and RPMI 8226, formononetin reduced the expression of cyclin D1 and cyclin B1 at 100 μM concentration. In ovarian cancer, formononetin decreased cell population at the G2-M phase and the Go-G1 phase in ES2 and OV90 cells. Similarly, it downregulated cyclin D1 and cyclin A, but also upregulation of CDK inhibitor, p21 protein expression in human non-small lung carcinoma in a dose-dependent manner [130]. Capsaicin arrest cell cycle at G0/G1 phase in esophageal carcinoma following the upregulation in p21 and downregulation of cyclin E, CDK4/6. Capsaicin inhibits cyclin D1 in colon cancer in a dose-dependent manner [131].

Hesperidin upturn p53 in breast, lung, and leukemia cell line in-vitro while in-vivo in colon cancer. Hesperetin upturn wildtype p53 in cervical adenocarcinoma SiHa cell

line and in-vivo in breast cancer. In vitro analysis shows that both hesperidin and hesperetin upregulate p21 expression and downregulate CKIs p21 and p27Kip1 [p27] in different cell lines [132]. Biochanin A potentially arrests the cell cycle at the G1, Go/G1, and G2/M phase. In vitro analysis shows that it enhances p21 expression while lowering cyclin B expression in PC-3 and LNCaP cells. Likewise, it also arrested cell cycles at different stages in different cell lines like G1 arrest in U87 glioma cells, S phase arrest in A549 cells, and G2/M phase in SW-480 colon cancer by increasing p53 and decreasing p21, cyclin A and CDK2 [133]. Ji et al. reported that Flavokawain B significantly induces G2/M arrest in osteosarcoma cells by increasing Myt1 levels and reducing cdc2, cyclin B1, and cdc25c. Similarly, in another article cell cycle at the same phase by reducing cyclin A, cyclin B1, Cdc2, and Cdc25C in KB cells of human squamous carcinoma cells [134].

1.3. Immunomodulatory and Anti-Inflammatory Potential of PCs

Chronic inflammation induces tumor, proliferation, metastasis, invasion, and angiogenesis pathways. Flavonoids are known for wide anti-inflammatory action via cytokines, chemokines, COX-2, pro-inflammatory transcription factors, inhibition of PI3K/Akt pathway, and NF-κB pathway. NF-κB family members [proteins] have a leading role in inflammatory and immune responses and evolutionary conserved proteins. The NF-κB signaling pathway is activated when ligands bind with receptors including BCR [B-cell receptor], TCR [T-cell receptor], Toll-like receptor, Tumor necrosis factor [TNF] superfamily and interleukin-1 receptor superfamily, bacterial and viral antigen, and UV radiation. Inflammation is mainly caused by deregulation of NF-κB. It is constitutively active in many cancers such as lymphoma, melanoma, pancreatic, ovarian, breast, and colon cancer. NF-κB signaling in cancer cells is involved in metastasis, cellular proliferation, angiogenesis, and invasion and prevents apoptosis. The immune system protects organisms from pathogens and related diseases. B lymphocytes, T lymphocytes, and macrophages protect the body and are helpful for immunity. Flavonoids inhibit the activity of mTOR and reduce T-cell differentiation. B cells, T cells, and macrophages cell surface consist of PD-1 [programmed cell death protein]. PD-L1 [programmed death-ligand 1] protein is present in cancer cells and binds with PD-1, a signal is processed to suppress the immune system. Thus, the inhibitors of PD-L1/PD-1 signaling pathway could be potential mediators in cancer immunotherapy [136].

Apigenin is a flavone that suppresses PD-L1 expression in A375 melanoma cells, whereas another potential compound in the family of flavanols which is quercetin inhibits PD-1/PD-L1 in in vitro cell lines. Similarly, two more compounds fisetin and glyasperin C which is isoflavonoid can inhibit this pathway. Isoflavone genistein exhibits the expression of several genes immersed in cell cycle regulation, migration, inflammation, and the PI3K/Akt and MAPK pathways in HeLa cells. Genistein put forth an influence on the expression of inflammatory-related genes in breast cancer MCF-7 cell lines [high ERa/ERβ ratio], T47D [low ERa/ERβ ratio], and MDA-MB-231 [ERa-negative] cell lines. In literature a study shows the effect of 2-10 μM of EGCG on Jurkat T cells, overexpressed the forkhead box P3 [Foxp3] and IL-10. 50 mg/kg of EGCG on Balb/c mice indicates increasing Treg number in lymph nodes, spleens, and pancreatic lymph nodes. Quercetin is also known for long-lasting anti-inflammatory phytochemicals with effective anti-inflammatory activity assessed in vitro and in vivo studies. Quercetin potentially induced anti-inflammatory effect in in-vitro studies, through suppression of LPS-induced TNF-a production in macrophages and LPS-induced IL-8 production in lung A549 cells. Additionally, quercetin treatment can reduce the production of [PI3K]- [p85], COX, and LOX [137].

1.4. Anti-angiogenesis, Anti-metastasis, Anti-invasive, and Anti-proliferative effects of PCs

PCs are potent agents and helpful in the suppression of cell proliferation. Evading growth suppression is another hallmark of cancer. This means that cancer cells can bypass programs that negatively regulate cell proliferation. Phenolic compounds especially the class of flavonoids reduce migration, angiogenesis, cell-matrix adhesion, and epithelial to mesenchymal transition EMT, it boosts cell-cell attachment and MET to suppress invasion and metastasis in different cancer and animal models. Most of the protein that is upregulated is mentioned here; γ-catenin, E-cadherin, MTA3, PAI-1, RECK, TIMP-1/TIMP-2, KAI1, PNII, alpha 1-AT, β1- integrin, cytokeratin-18, and OPG while some of them are downregulated which are; MMP-2, -3, -7, -9, -12, MT1-/MT2/ MT3-MMP, uPA, tPA, uPAR, MUC1, vitronectin, fibronectin, vimentin, snail, VEGF, EGFR, VASP, EGF, ErbB2/ErbB3, PSA, EMMPRIN, Met [HGFR], VEGR-R2, HIF-1a, β1-/β4- integrin, a5-/β1-/av-/β3-integrin receptors, β-catenin, angiopoietin1/2, CXCR4, CXCL12, OPN, mdm2, COX-2, claudin, PGE2, iNOS, plamin activation, vWF, PECAM-1 [CD31], RANKL, and osteoclast, these protein are involved

in biological alterations. Phenolic compound changes the expression of these candidate results in promoting IkB-a, FOXO3, and ERa suppressed the pathways involved in signaling of Ras, Raf, MEK4, ERK, JNK, p38, MAPKAPK2, HSP27, PKC, FAK/cSrc/p130Cas, FAK/cSrc/paxillin/Gab-1/GRB-2, Rac1, PI3K/Akt, mTOR, p70S6K, AP-1, NF-kB, STAT3, ZEB1, and SLUG. These signaling molecules and various transcription factors are involved in the modulation of invasion, metastasis, and angiogenesis in cancer cell lines [138].

Moreover, polyphenols, present in green tea, can inhibit angiogenesis and therefore, limit the growth of the tumors or prevent tumor invasion through inhibition of the MMP [matrix metalloproteinases]. Catechin inhibits angiogenesis by regulating pro and anti-angiogenic factors, such as pro-inflammatory cytokines, Nitric oxide, IL-2, and VEGF. Curcumin, resveratrol, EGCG, Luteolin and Butein inhibit the angiogenic factor VEGF in tumor cells. Apart from this, quercetin suppresses angiogenesis through multiple mechanisms, including interaction with the COX-2, EGFR, the HER2 intracellular signaling pathway, lipoxygenase-5 enzymes, and the NF-κB. EGCG inhibits the thrombin-induced invasion of Hep3B hepatoma cells by suppressing p42/p44 MAP kinase [ERK1/2] activation. In HepG2, EGCG inhibits cell invasion into the basement membrane by lowering the MUC1, MMP-2, and MMP-9 protein expression. EGCG inhibits MMP-2/MMP-9 and suppresses MMP-2 and MT1-MMP in rat hepatic stellate cells SK-Hep-1. A similar study explains that 10μM EGCG eliminates ROS-mediated invasion and adhesion of the rat ascites hepatoma cell line AH109A. EGCG downregulated the expression of MMP-9 and suppressed the localization of NF-κB in lung carcinoma 95-D cells. In BZR bronchial tumor cells, it also inhibited migration and the expression of vimentin and MMP-2 suggesting that it could be a potential candidate to treat lung cancer invasion. Silibinin anti-metastasis effect was found in C57BL/6 mice-bearing Lewis lung carcinoma [LLC] cells and in TRAMP mice, where it decreased MMPs, snail-1, vimentin, fibronectin and upregulate E-cadherin [138]. In human PC3-M PCa cells, which were implanted in mice, genistein suppresses lung metastasis, cell-to-cell adhesion, and the ratio of phosphorylated/total FAK, HSP27, and p38 [139]. In literature, EGCG suppresses angiogenesis and related markers like VEGF, and CD31 [128].

2. Anti-oxidative Potential of PCs

Production of reactive oxygen species [ROS] and free radical accumulation depends upon pro-oxidant and antioxidant activities. ETC in mitochondria, mainly oxidative phosphorylation, is the major site of ROS production. ROS generation produces oxidative stress leading to the development of inflammation and cancer [11]. Flavonoids act as a double-edged sword, in cancer cells; they act like pro-oxidants and antioxidants under normal conditions of cells.

Daidzein is involved in cell cycle arrest and reactive oxygen species ROS generation in breast cancer cell lines [140]. Hesperetin a flavanone, which fights against many cancers, induces apoptosis by increasing ROS generation [132]. Naringenin is another compound belonging to the family of flavanone, a promising anticancer compound that induced ROS generation in JAR and JEG 3 cell lines [choriocarcinoma] [141]. Another study discuss the same cascade in human epidermoid carcinoma A431 cells [142], while in prostate cancer PC3 and LNCaP cells it exerts its effects through proliferation and migration inhibition [143]. Pterostil upregulates ROS generation in PC9 and A549 within an effective concentration of 20–60 μM [46]. It can also upregulate ROS in esophageal cancer EC109 cell line at an effective dose of 50-150 μM [47]. Silibinin generate ROS in HCC HepG2 cell lines and reduce GSH production at 50–200 μM concentration [68]. As mentioned earlier about the role of quercetin in apoptosis, inhibition of metastasis, cell proliferation and invasion, it can also play a central role in regulation of oxidative stress. Some recent studies denoted that it could reduce proliferation in hepatocellular carcinoma HepG2 cell lines and decrease intracellular ROS level [144]. In human breast cancer cell line MCF-7 [89] and human gastric cancer AGS cell lines [145], it increases the production of ROS.

Another important compound, kaempferol, modulates ROS level and induces apoptosis in bladder carcinoma cells. ROS generation activated caspase cascade and stimulated apoptosis in HCT116, HCT15, and SW480 cancer cell lines. However, ROS mediated mitochondrial apoptosis observed in rat hepatocellular carcinoma cells by kaempferol [11]. Apigenin also induced ROS mediated mitochondrial apoptosis in human cervical cancer cell lines including HeLa [human papillomavirus/HPV 18-positive], CaSki [HPV 16 and HPV 18-positive], SiHa [HPV 16-positive] and C33A [HPV-negative] cells [146]. In ovarian cancer cell lines A2780,

OVCAR-3 and SKOV-3, apigenin and luteolin [flavones] modulate ROS level and induce apoptosis. Flavone chrysin also augment ROS and lipid peroxidation levels, leading to the death of choriocarcinoma JAR and JEG3, ovarian cancer [ES2 and OV90] cells, and bladder cancer. Thus, valuable data suggest the beneficial effects of flavonoids as potent antioxidants and pro-oxidants under normal and pathological conditions, capable of triggering apoptosis and controlling proliferation and inflammation [11].

3. Antidiabetic effect of PCs

Blood glucose level is maintained by insulin; β-cells of the pancreas produce insulin hormone which lowers glucose levels in the blood. The Problems in insulin production and sensation cause diabetes mellitus [DM]. There are two types of diabetes Type 1 and Type 2 DM, in T1DM, the body's immune system attacks on islet cells of the pancreas and the pancreas doesn't make insulin while in T2DM, the body cells don't respond to insulin. T2DM is a more common disease characterized by insulin resistance, hyperglycemia, β cell dysfunction, and pancreatic amyloid accumulation. T2DM is the leading cause of death worldwide and high mortality rate. Currently, existing disease-modifying therapies for T2DM are not sufficient to eradicate the disease from the world, though some drugs can just treat the symptoms, not the exact underlying mechanism, which may be related to amyloid accumulation, ROS, or exposure to elevated free fatty acids [FFA], glucose or pro-inflammatory cytokines, ER stress, and mitochondrial dysfunction. PCs could be promising agents for the treatment of various pathological disorders, together with type 2 diabetes mellitus [T2DM]. Past literature shows evidence of antidiabetic activity of PCs in vitro, in-vivo, and in certain clinical trials [147].

Cytotoxic human amylin [hA] accumulates and provokes cytotoxicity in pancreatic islet β cells and causes disruption of these cells. Along with this their role in oxidative stress and inflammation is pronounced. Polyphenols significantly show antidiabetic effects because of their ability to inhibit hA accumulation and modulate ROS and inflammation which can protect β-cells. Recent research suggests that polyphenol exerts its effects via reducing ROS, inflammation, and cellular pathways; this may have beneficial effects on β-cell survival and insulin sensitivity [147].

The use of polyphenols in traditional medicines because of their potential health benefits draws the attention of modern scientists toward their use against multiple

diseases, especially diabetes mellitus. EGCG, resveratrol, curcumin, etc. show strong antidiabetic effects. Clinical trials have revealed some hopeful but controversial results. The supreme challenge to achieve a consistent therapeutic effect may be due to a lack of understanding of the molecular basis of polyphenol action, along with the complexity of multifactorial diseases such as T2DM. Natural polyphenols remain an active area of research for many diseases. Improved research techniques will enable us to understand the exact mechanism of disease and the exciting use of these multifunctional compounds [147].

In-vitro study suggests the protective effect of polyphenols against cytotoxicity induced by hA treatment in multiple pancreatic cell lines. hA-induced cytotoxicity INS-1E rat insulinoma cell line is prevented by Resveratrol [148,149]. At the same time, Hernandez et al. observed a decrease in ROS in hA-overexpressing INS-1E cells [150]. Meng et al. noticed the hA-induced toxicity in INS-1 cells prevented by EGCG [151]. Lopez et al. and Daval et al. demonstrated the preventive effect of quercetin and curcumin on RIN-m5F rat insulinoma cells and INS 832/13 β-cell line respectively [152, 153]. The Cyto-protective effect of Oleuropein against hA in INS-1 cells. Similarly, baicalein inhibits hA-induced cytotoxicity in INS-1 cells [154]. At the same time, Rosmarinic acid produced non-toxic aggregation of hA in INS-1 cells where it neutralized hA-induced cytotoxicity [155].

In-vivo data suggests the protective effect of polyphenols against various animal models. In db/db mice it was observed that resveratrol supplementation can decrease blood glucose and HbA1c, increased plasma and pancreatic insulin [156], and glucose tolerance is enhanced [157]. Resveratrol also increases insulin levels in NA-STZ-treated mice [158]. EGCG decreased hyperglycemia in STZ-treated mice when administered intraperitoneal [159], and decreased blood glucose levels in Zucker rats and Sprague Dawley rats [160]. On the other hand, long-term administration of EGCG lowers blood glucose levels in db/db mice [161].

Epicatechin present in green tea also shows mixed results when treated with alloxan-induced diabetes in mice. However, some results were in favor of it where it helps to regenerate β cells and normalize blood glucose levels [162]. Quercetin lowered plasma glucose levels when orally administered in alloxan-induced diabetes in STZ rats [163], mice, and rats fed a high-cholesterol diet [164], and mice [165] and lower plasma glucose levels when administered intraperitoneally in STZ-rats [166].

Clinical trial has the same conflict, for example, past studies on the major green tea polyphenol show that a 300mg/day dose of EGCG reduced fasting blood glucose level even if there was no change in insulin level [Ha19]. On the other hand, an 800 mg/day dose in obese participants results in no change in blood fasting glucose level, insulin, and HbA1c [167]. A similar case happens with resveratrol, where a low dose of resveratrol 10mg/day supplemented to T2DM decreased HOMA-IR but had no effect on insulin level [168]. Goh et al. describe that even a high dose of 3 g/day with T2DM didn't show any change in HOMA-IR [169]. Likewise, a 5-week intervention involving the administration of 1 g/day of resveratrol showed no discernible alteration in either fasting or post-prandial blood glucose levels or HbA1c, as per the findings of Thazhath et al. [170]. Similarly, in a study involving obese participants, Poulsen et al. observed no significant impact of a 4-week regimen of 1,500 mg/day resveratrol on insulin resistance, fasting glucose levels, or insulin levels [171]. These results stand in contrast to those reported by Timmers et al. where a 30-day treatment with 150 mg/day of resveratrol led to reductions in fasting plasma glucose, insulin levels, triglycerides, and HOMA-IR. Even trials longer than a specific time limit show no significant result [172]. Supplementation for a longer time, these trials have no significant result. As per the findings of Bo et al. even after a 6-month trial in type 2 diabetes mellitus patients, there was no change found in serum glucose, HOMA-IR, insulin, C-peptide, HbA1c [173].

A similar finding found that in patients having T2DM and hypertension, 12 months' exposure to a low dose of resveratrol didn't affect serum glucose, several inflammation markers, HbA1c [174]. Curcumin exerts a potential effect, in reported literature, 12 weeks of curcumin in T2DM lowered serum insulin level, serum glycogen synthase kinase-3β, hA expression [175]. Quercetin another phenolic compound, when 250 mg/day supplemented for 8 weeks in DM patients, no change was found in fasting blood glucose, HbA1c levels, insulin levels, and insulin sensitivity or blood lipid profile but increased serum total antioxidant capacity [176].

4. Antibacterial Activity of PCs

Antibiotic resistance is a global problem that affects humans, animals, the economy, and the environment equally. Many clinically concerned bacteria have been reported to be resistant to different antibiotics, and this fact is arising as one of the major hazards to public health. Surveillance efforts conducted across diverse

geographical regions have revealed the evolutionary trajectory of many infectious microorganisms over time, with a concerning proliferation of antibiotic-resistant species capable of evading the inhibitory effects of these agents. Notably, this escalating resistance phenomenon is not confined to a singular microbial species but encompasses a myriad of additional pathogens, including viruses, fungi, and protozoa. The classification of multidrug resistance [MDR] encompasses primary, secondary, and clinical resistance categories. Primary resistance manifests when an organism has never encountered the specific drug of interest within a particular host, indicative of resistance to any antibiotic before the initiation of the initial eradication regimen. Secondary resistance, also termed "acquired resistance," emerges in an organism after exposure to antimicrobial agents, signifying resistance to antibiotics in patients who have previously undergone at least one unsuccessful eradication attempt [177].

Secondary resistance is further delineated into intrinsic and extensive categories. Intrinsic resistance denotes the innate insensitivity of all microorganisms within a single species to certain commonly prescribed first-line agents, which are administered based on clinical evidence, exemplified by the emergence of rifampicin resistance in Mycobacterium tuberculosis [178]. Clinical resistance denotes the scenario wherein infecting organisms are inhibited by antimicrobial concentrations associated with a high probability of therapeutic failure or infection recurrence within a host due to compromised immune function. This condition arises when the pathogen is inhibited by antimicrobial concentrations exceeding what can be safely achieved through standard dosing [177, 179]. The pervasive phenomenon of antibiotic resistance has emerged as a pressing public health concern, necessitating urgent efforts to develop alternative therapeutic agents capable of addressing MDR. Pathogens may acquire resistance through single or multiple mechanisms, including plasmid-based genetic mutations, antibiotic inactivation, target site modifications, biofilm formation, prevention of drug uptake, efflux of drug compounds, enzymatic degradation, quorum sensing, bacterial toxins, and virulence factors [179].

As per the report of the World Health Organization [WHO], mortalities caused by antibiotic resistance will be the leading cause of death worldwide by 2050, if preventive measures are not taken immediately. Therefore, there is a dire need to develop novel drugs to overcome the burden of bacterial antibiotic resistance

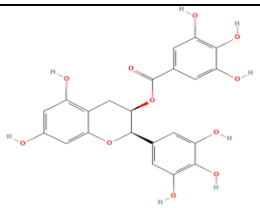
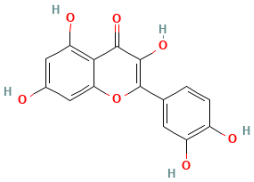
[180]. Bioactive compounds extracted from various natural resources, including plants, have been successfully used in the treatment of various diseases. A plethora of studies have reported that various plant-derived compounds such as paclitaxel, vinblastine, camptothecin, vincristine, and podophyllotoxin are used to treat different disorders due to their lower harmful effects, low cost, high abundance in different plant species, and their ability to regulate multiple signaling pathways simultaneously [181,182]. Today, even many extracts of multiple plants show a great variety of benefits for humans. It has been reported that most of the extracts contain polyphenols, which are compounds containing one or more phenolic groups [180]. In parallel to different bioactivities of polyphenols, the strong antibacterial activity of polyphenols has also been reported in multiple studies [180].

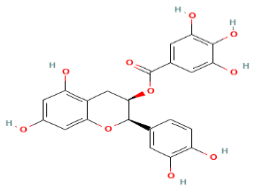
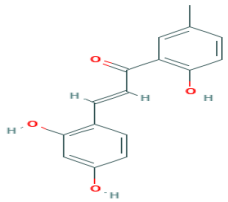
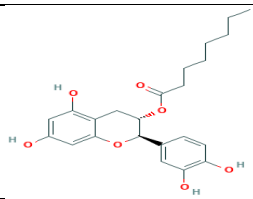
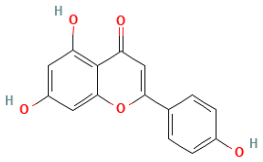
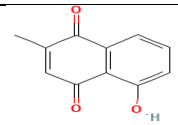
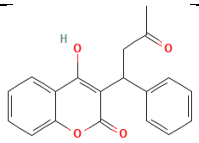
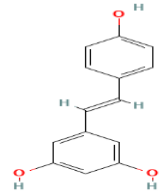
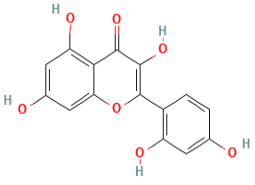
Polyphenols have a strong potential to exert antimicrobial effects at very low dose concentrations. Polyphenols contain one or more aromatic rings attached to several hydroxyl groups. Polyphenols are synthesized from 2 aromatic amino acids - phenylalanine and tyrosine. As secondary metabolites of various plants, their number is estimated to be approximately 10 % of the plant's secondary metabolites. These phytochemicals are key players in providing the defense to plants against viruses, bacteria, insects, fungi, and herbivores [183]. The antimicrobial mechanism of action of most of the polyphenols is described in Table 3. It is reported that the OH group of polyphenolics is the main cause of the antibacterial activity of polyphenols [184, 185]. The OH can mainly target the bacterial cell membrane by interacting with it via hydrogen bonds, that either result in the description of the cell membrane leading to leakage of cellular content or [186] causing the delocalization of electrons [because of the double bonds of the aromatic nucleus], leading to depolarization of bacteria [acting as proton exchangers] and thus change the proton motive force, decreasing the level of ATP pool and lowering the pH gradient throughout the membrane. Such cascade of reactions, induced by the OH leads to bacterial cell death [185]. The presence of an alkyl function group in the aromatic nucleus produces phenoxyl radicals reported to increase the antibacterial activity of phenolics and may change their distribution between non-aqueous and aqueous phases, even in bacterial phases too [186]. The presence of acetate in the structure of PCs can increase the bioactivity of these compounds by either the OH as a protein denaturing agent or enhancing their electronegativity due to the aldehyde functional groups increasing electron transfer and chemical reactions with the

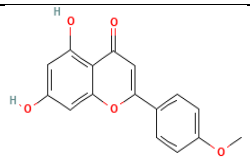
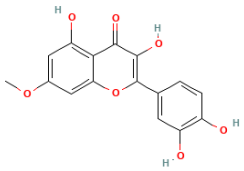
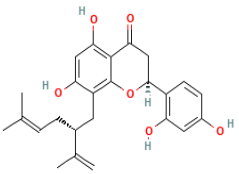
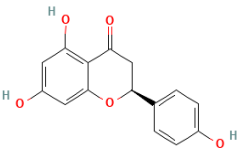
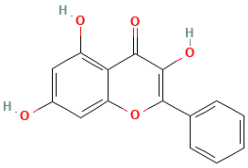
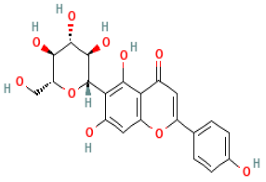
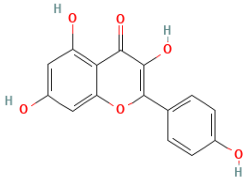
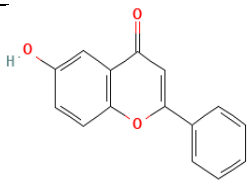
proteins of the membrane [187]. The occurrence of galloyl moiety in PCs can also cause damage to the structure of the membrane, thus promoting the antibacterial potential of epigallocatechin gallate particularly against Gram-positive bacteria [188]. In addition to the structure and chemical composition, the lipophilic properties of phytocompounds also play a pivotal role in their antibacterial activity [186].

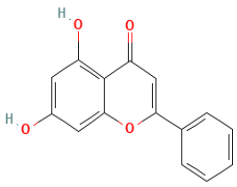
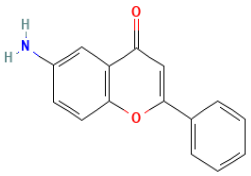
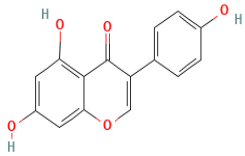
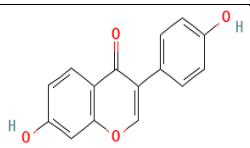
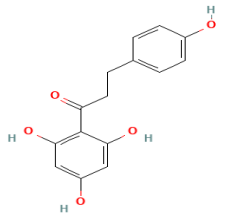
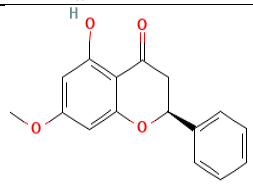
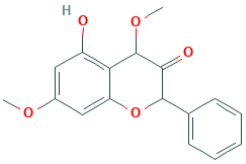
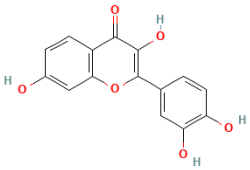
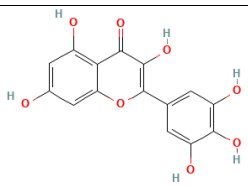
Literature suggests that the antimicrobial action of phenolics increases with the increase in their lipophilic character; this may be related to their strong interactions with the plasma membrane due to their lipophilic character [188]. Furthermore, it is also reported that flavonoids with lipophilic character which are highly hydroxylated can be more disrupting for membrane structure. It is suggested that differences in the distribution and number of hydroxyl groups, the degree of polymerization, as well as the occurrence of methoxy groups in the C ring of polyphenols, can influence the degree of interactions that occur between various compounds and lipid bilayers. Moreover, flavonoids with no hydroxyl on their B Rings are more effective for the destruction of microbial membranes than those that have –OH [189].

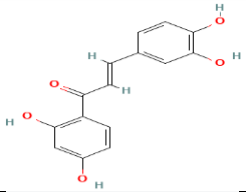
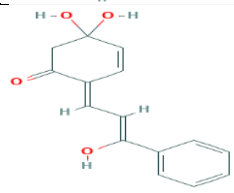
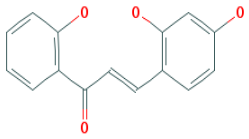
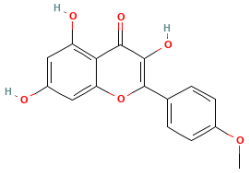
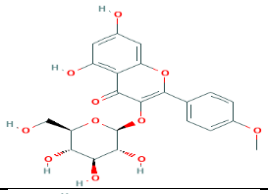
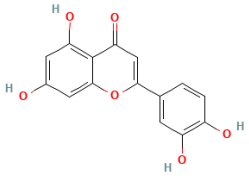
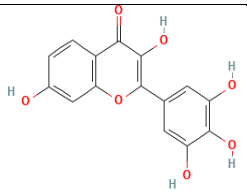
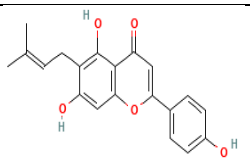
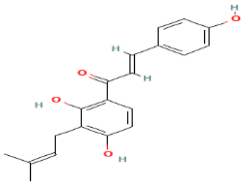
Table 3 Describing the antimicrobial activity of different polyphenols

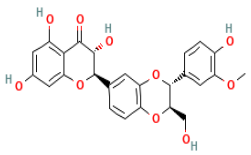
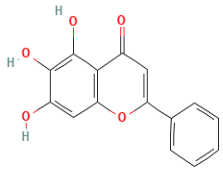
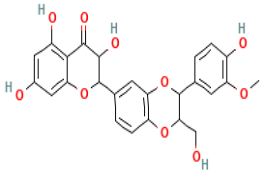
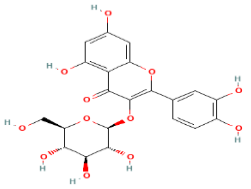
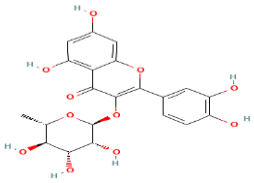
Chemical Name	Structural Formula	Mechanism of Action	References
Epigallocatechin Gallate [EGCG]		Inhibiting the activity of F1FO ATPase	[189]
		Inhibit biofilm formation	[190]
		Reduced the activity of different reductases [FabG, FabI]	[191]
		Inhibit the activity of enzymes [3-ketoacyl-ACP reductase and enoyl-ACP reductase] involved in the formation of fatty acids and synergistically reduce the synthesis of peptidoglycan. It also reduces the DHFRs	[189]
		Lowers the synthesis of DNA, RNA, and protein	[192]
Quercetin		Increases the permeability of bacterial cell membranes	[193]
		Decreases proton-motive force and inhibits the activity of D-alanine-D-alanine ligase	[189]

		Inhibit FAS-I.	[194]
[−]-Epicatechin Gallate		Induces a reduction in the fluidity of the membrane Increases the leakage of intracellular substances such as ions and different proteins	[195] [196]
2,4,2′-trihydroxy-5′-methylchalcone		Induces a reduction in the fluidity of the membrane	[195]
3-O-octanoyl-[+]-catechin		Induces a reduction in the fluidity of the membrane	[195]
Apigenin		Inhibiting the activity of hydroxyacyl-acyl carrier protein dehydratase and DNA gyrase Destabilization of the membrane by disorienting and disordering the lipids of the membrane Inhibits the activity of D-alanine-D-alanine ligase Inhibiting the DNA gyrase isolated from *E. coli*	[186] [197] [189] [198]
Plumbagin		Disrupt potential efflux pumps	[214]
Coumarins		Reducing cell respiration	[186]
Resveratrol		Reducing cell respiration and interfering with the cell cycle of bacteria	[186]
Morin		Induced destabilization of the membrane by disorienting and disordering the lipids of the membrane Inhibit FAS-I	[197] [194]

		Inhibited the replicative helicases such as RecBCD and DnaB nuclease/helicase Inhibiting the activity of F1FO ATPase	[199] [189]
Acacetin		Destabilization of the membrane by disorienting and disordering the lipids of the membrane	[197]
Rhamnetin		Destabilization of the membrane by disorienting and disordering the lipids of the membrane	[197]
Sophoraflavanone G		Lowering the fluidity in hydrophobic and hydrophilic regions of both the outer and inner cellular membranes	[200]
Naringenin		Lowering the fluidity in hydrophobic and hydrophilic regions of both the outer and inner cellular membranes	[200]
Galangin		Induced pseudo multicellular aggregates when incubated with *S. aureus* Reverse the resistance against amoxicillin via inhibition of ribosome synthesis and peptidoglycan	[201, 202] [189]
Isovitexin		Inhibits the biofilm formation in *S. aureus* and *S. mutans*	[203, 204]
Kaempferol		Inhibits FAS-I Inhibited DNA gyrase isolated from *E. coli*	[194] [205]
6-hydroxyflavone		Inhibited the biofilm formation	[206]

Chrysin		Inhibited DNA gyrase isolated from *E. coli* Inhibited the biofilm formation	[205] [206]
6-aminoflavone		Inhibited the biofilm formation	[206]
Genistein		Inhibited the biofilm formation	[206]
Daidzein		Inhibited the biofilm formation	[206]
Phloretin		Inhibited the biofilm formation Lowered the fimbriae formation and reduced the expressions of 2 toxin genes [hemolysin hlyE and Shiga toxin 2 stx2]	[206] [207]
Pinostrobin		Increased the permeability of the membrane and inhibit biofilm formation	[189]
5-hydroxy-4',7-dimethoxyflavanone,		Inhibits bacterial growth by lowering the level of transacylase fabD [malonyl CoA-acyl carrier protein] that controls bacterial FAS-II	[208]
Fisetin		Inhibit FAS-I Inhibits FAS-II	[194] [209]
Myricetin		Inhibited the replicative helicases such as RecBCD and DnaB nuclease/helicase Inhibits FAS-I Potential inhibitor of RNA and DNA polymerases, as well as reverse transcriptase	[199] [194] [210, 211]

		Powering the synthesis of DNA, RNA, and protein	[192]
Butein		Inhibits FAS-II	[209]
4,2',4'-trihydroxychalcone		Inhibits FAS-II	[209]
Isoliquirtigenin		Inhibits FAS-II	[209]
kaempferide		Reverses the resistance against amoxicillin via inhibition of ribosome synthesis and peptidoglycan	[189]
kaempferide-3-O-glucoside		Reverses the resistance against amoxicillin via inhibition of ribosome synthesis and peptidoglycan	[189]
Luteolin		Inhibited the replicative helicases such as RecBCD and DnaB nuclease/helicase Can inhibit FAS-I	[199] [194]
Robinetin		Lowering the synthesis of DNA, RNA, and protein	[192]
6-prenylapigenin		Induces membrane depolarization that can affect the energy production in bacteria and ultimately lead to bacterial cell death	[212]
Isobavachalcone		Induces membrane depolarization that can affect the energy production in bacteria and ultimately lead to bacterial cell death	[212]

Silibinin		Reduces ATP hydrolysis but are not effective in reducing ATP synthesis	[189]
Baicalein		Can inhibit FAS-I	[194]
Silymarin		Inhibitor of *E. coli* F1FO ATPase silymarin	[189]
quercetin-3-glucoside		Reduces ATP hydrolysis but are not effective in reducing ATP synthesis	[189]
quercetin-3-O-rhamnoside		Reduces ATP hydrolysis but are not effective in reducing ATP synthesis	[189]

Phenylpropanoids may cause damage to the cell membrane and even inhibit the activities of enzymes by binding them. At the same time, phenolic acids have a strong potential to destroy membrane integrity, which results in the leakage of intracellular constituents. Flavonoids lead towards the formation of different complexes by binding with various proteins within the cell wall of bacteria [186]. Quercetin is a flavonoid that increases the permeability of bacterial cell membranes [193]. In addition to quercetin, several other flavonoids like [−]-epicatechin gallate, 2,4,2′-trihydroxy-5′-methylchalcone, [−]-epigallocatechin gallate, and 3-O-octanoyl-[+]-catechin, can induce a reduction in the fluidity of the membrane [195].

Furthermore, flavonoids may disrupt energy metabolism and inhibit DNA synthesis, thus reducing the formation of RNA and protein in bacteria [213]. Few flavonoids, like apigenin, show their antibacterial effect by inhibiting the activity of hydroxyacyl-acyl carrier protein dehydratase and DNA gyrase [186]. Catechins also show antibacterial activities by inhibiting the activity of DNA gyrase [195]. Naphthoquinones such as plumbagin are reported to disrupt potential efflux pumps

in Gram-negative bacteria, which are mostly resistant to various antibacterial drugs due to efflux pumps [214] Coumarins show antibacterial effects by reducing cell respiration [186]. Paulo et al. reported the bacteriostatic effect of 200mg/L resveratrol [4 × minimal inhibitory concentration [MIC]] for Bacillus cereus and 2 × MIC for Staphylococcus aureus [215]. Investigations also suggested that resveratrol can also interfere with the cell cycle of bacteria as evidenced by modifications in the morphology of bacteria and DNA upon the treatment of resveratrol [186].

It is important to note that catechins and other flavonoids can damage the bacterial membrane, leading to the inability of the bacteria to secrete different toxins [189]. Catechins show their antibacterial effect by interacting with the lipid bilayer, rupturing the bacterial membrane, and inhibiting the formation of extracellular and intracellular enzymes [216]. Fathima and Rao suggested that catechins kill bacteria by enhancing the production of ROS which disrupts the permeability of the cell membrane and liposome membrane [217, 218]. Fascinatingly, liposomes that have a high concentration of negatively charged lipids were less vulnerable to the damage induced by catechin, just as catechins have a low inhibitory effect on Gram-negative bacteria due to the presence of negatively charged lipopolysaccharides of the outer membrane. This information correlates well with the literature suggesting lower antibacterial potential of catechins against Gram-negative bacteria as compared to Gram-positive bacteria. It has been reported that membrane disruption due to catechins results in leakage of potassium in methicillin-resistant Staphylococcus aureus [MRSA] strain, which is the first sign of membrane damage in bacteria. They have also observed that increased lipophilic, acylated to 3-O-octanoyl- epicatechin results in better antibacterial effects, than unmodified epicatechin. The modification in epicatechin increased the membrane affinity of their large acyl chains, resulting in an increased antibacterial effect [189]. Sato et al. suggested that treatment of Streptococcus mutans with 2,4,2'-trihydroxy-5'-methylchalcone increases the leakage of intracellular substances such as ions and different proteins [196]. Quercetin derived from propolis effectively decreases proton-motive force in S. aureus and thus contributes to the synergistic effect of propolis with clinically used antibiotics, such as ampicillin and tetracycline [189]. Furthermore, Ollila et al. showed that morin, acacetin, apigenin, and rhamnetin induced destabilization of the membrane by disorienting and disordering the lipids of the membrane [197]. Tsuchiya and Iinuma claimed that sophora flavanone G

and naringenin show antibacterial potential against MRSA by lowering the fluidity in hydrophobic and hydrophilic regions of both the outer and inner cellular membranes [200].

The potential of bacteria to grow as a biofilm plays a key role in increasing the rate of bacterial infections as well as increasing bacterial resistance against antimicrobial drugs [189]. To date, the approaches to eliminating the biofilm bacteria by using antibiotic agents are very limited therefore there is a dire need to find novel antibacterial agents that can lower the bacterial biofilms induced drug resistance. Interestingly, different polyphenols such as galangin, 3-O-octanoyl-epicatechin, and EGCG induced pseudo multicellular aggregates when incubated with S. aureus [201, 202]. However, it has been observed that polyphenols inhibited the growth of bacteria after aggregation. It is believed that polyphenols induced bacterial aggregation by partially breaking down the bacterial cell wall. This results in the fusion of bacterial cell membranes leading to the reduction in the uptake of nutrients due to a reduction in surface area, therefore it cannot be said that polyphenols increase biofilm formation, in fact plethora of literature suggested that polyphenols inhibit biofilms [189]. Isovitexin, and 5,7,40-trihydroxyflavanol strongly inhibit the biofilm formation in S. aureus and S. mutans [203, 204]. Citrus flavonoids, such as kaempferol, quercetin, naringenin, and apigenin are efficient antagonists of cell–cell signaling [219].

In addition to these some flavones, such as 6-hydroxyflavone, apigenin, chrysin, 6-aminoflavone, as well as isoflavones like genistein, and daidzein, and a dihydrochalcone such as phloretin inhibited the biofilm formation of E. coli O157:H7 [206]. Furthermore, phloretin [a natural, flavonoid] without affecting the planktonic cells, triggered the reduction of enterohemorrhagic E. coli O157:H7 biofilms. This is a prominent feature of phloretin as a biofilm inhibitory agent that should selectively kill the pathogenic strains without affecting the commensal microflora [189]. Fimbriae, including pili and curli, are key factors for the formation of biofilm [220]. Phloretin significantly lowered the fimbriae formation in E. coli O157:H7, by suppressing the genes involved in curli formation [csgA and csgB]. This study also suggested that phloretin reduced the expressions of 2 toxin genes [hemolysin hlyE and Shiga toxin 2 stx2]. However, it also increased stress resistance genes, such as hcsBA, and marRAB genes [207]. Thus, phloretin can lead to antibiotic resistance as well. Inhibitors of

efflux pumps [IEP] are reported not only to inhibit the efflux pumps but also to block the biofilm formation [221].

Pinostrobin [a dietary flavanone discovered in the wood of pine, Pinus strobus] increased the permeability of membrane in both Gram-negative and Gram-positive bacteria [E. faecalis, S. aureus, E. coli, and P. aeruginosa], which directly related with its effect on IEP and formation of antibiofilm in Gram-negative bacteria. This study also suggested the antibiofilm activity of pinostrobin is not IEP dependent and thus will not be involved in repressing the genes responsible for curli [189]. Tea EGCG is an effective antimicrobial agent against both the planktonic and biofilm forms of E. faecalis. It reduces bacterial growth and downregulates the expression of genes regulating biofilm formation [190]. Bacterial-type II fatty acid synthase [FAS-II] is an excellent target for killing the bacteria as it is much different from the mammalian FAS-I. Multiple studies have suggested that polyphenols can strongly inhibit the FAS-II components [189]. Elmasri et al. noticed that 5-hydroxy-4',7- dimethoxyflavanone, and 5,6,7,4',5'- pentahydroxy flavone can inhibit bacterial growth by lowering the level of transacylase fabD [malonyl CoA-acyl carrier protein] that controls bacterial FAS-II [208]. Furthermore, EGCG reduced the activity of different reductases [FabG, FabI] in the bacterial FAS-II [191]. FabG enzyme can also be a potential target for the development of new antibacterial drugs as it participates in the biosynthesis of fatty acid and is the only reported isoenzyme to carry the reduction of the beta keto groups of bacterial membranes. EGCG can also inhibit the activity of other enzymes [3-ketoacyl-ACP reductase and enoyl-ACP reductase] involved in the biosynthesis of fatty acids. Infection with mycobacteria can result in different severe disorders that can be difficult to treat [189]. Mycolic acids found in the bacterial cell wall of mycobacteria are the most distinguishing and essential feature that plays a vital role in the survival of mycobacteria. Interestingly, both FAS-I and FAS-II are important for the synthesis of mycolic acid. Several polyphenols such as luteolin, baicalein, EGCG, quercetin, fisetin, myricetin, morin, and kaempferol can inhibit FAS-I [194]. Moreover, some of these inhibit the activities of FAS-II components as well [enoyl-ACP-reductase, b-ketoacyl-ACP reductase, and b-hydroxyacyl-ACP dehydratases]. Furthermore, Brown et al. noticed that fisetin, butein, 4,2',4'-trihydroxychalcone, isoliquirtigenin show inhibitory effect against FAS-II isolated from Mycobacterium bovis BCG. Peptidoglycan basic constituent of the bacterial cell wall is also a major target for antibacterial drugs [209].

Flavonols such as kaempferide, galangin, and kaempferide-3-O-glucoside not only showed antibacterial activity against amoxicillin-resistant E. coli, but these compounds also can reverse the resistance against amoxicillin via inhibition of ribosome synthesis and peptidoglycan. Another study explained that catechins bind with the layer of peptidoglycan thus disrupting the synthesis of the bacterial cell wall. DL-cycloserine and EGCG synergistically reduce the synthesis of peptidoglycan. Kinetic studies of apigenin and quercetin showed that these compounds could inhibit the activity of D-alanine-D-alanine ligase [responsible for producing the terminal dipeptide of peptidoglycan precursor UDPMurNAc-pentapeptide]. However, quercetin's inhibitory effect is quite lower than apigenin due to its additional -OH groups that increase its affinity to the enzyme. DNA gyrase is another important target for the development of novel antibacterial drugs that have a key role in the replication of DNA [189]. Ohemeng et al. observed that apigenin, quercetin, and 3,6,7,3',4'-pentahydroxyflavone showed antibacterial activity by inhibiting the DNA gyrase isolated from E. coli [198].

In silico studies recommended that quercetin mainly targeted the subunit B of DNA gyrase from Mycobacterium tuberculosis, and M. smegmatis [222]. This was further confirmed, by the other studies which also suggested that quercetin strongly binds with the B subunit of gyrase and blocks the ATP binding cavity by making Hydrogen interactions via 5, 7, and 3' –OH groups to the residues of DNA gyrase [223]. This is correlated with the findings of Wu et al. [224] that suggested the inhibition of the ATP binding cavity of D-alanine-D-alanine ligase by the previously discussed flavonoids [224]. Moreover, some other compounds such as kaempferol, and chrysin completely inhibited DNA gyrase isolated from E. coli [205]. Helicases also play a key role in the replication of DNA by separating and rearranging the DNA duplexes in reactions supported by the hydrolysis of ATP [225]. Luteolin, myricetin, and morin inhibited the replicative helicases such as RecBCD and DnaB nuclease/helicase of E. coli [199]. Among all these, myricetin has been reported as a potential inhibitor of Gram-negative bacteria, multiple RNA and DNA polymerases, as well as reverse transcriptase [210, 211]. Dihydrofolate reductase [DHFR] is an enzyme involved in the pathway of folic acid synthesis, which is a source of precursors for purines and pyrimidines [226]. EGCG has been described to reduce the DHFRs from M. tuberculosis, Streptomonas maltophilia, and E. coli. Moreover, EGCG has also been reported to exhibit synergistic effects with other clinically used inhibitors of folic acid

synthesis, such as ethambutol and sulfamethoxazole [189]. Mori et al. observed that incubation with myricetin, robinetin, and EGCG resulted in lowering the synthesis of DNA, RNA, and protein by S. aureus and Proteus vulgaris [192]. Dzoyem et al. reported that exposure to S. aureus with 6-prenylapigenin, and isobavachalcone leads to membrane depolarization that can affect the energy production in bacteria and ultimately leads to bacterial cell death [212]. Furthermore, Haraguchi et al. suggested that licochalcones isolated from Glycyrrhiza inflata reduced the consumption of oxygen in Micrococcus luteus cells, and the mechanistic study reported that the site of inhibition that lowers the consumption of oxygen may be between Co Q and cytochrome c in the electron transport chain of bacteria. ATP synthase is the most conserved enzyme with 2 sectors, FO and F1. In E. coli, FO consists of ab2c10 while F1 consists of a3b3cdeab2c10 [213]. ATP synthesis and hydrolysis occur on 3 catalytic sites in the F1, whereas in FO movement of the proton takes place [227]. The literature describes that a range of polyphenols can attach at the polyphenol binding site [a, b, and c-subunits of the F1 sector] and can reduce the activity of the ATP synthase. Therefore, bacterial growth can be easily reduced by targeting the activity of ATP synthase [228].

The most efficient inhibitors of E. coli F1FO ATPase are silibinin, baicalein, morin, EC, and silymarin. Furthermore, quercetin-3-glucoside, quercetin, and quercetin-3-O-rhamnoside are known to reduce ATP hydrolysis but are not effective in reducing ATP synthesis. EGCG effectively inhibited the aciduric and acidogenic activities of S. mutans, by inhibiting the activity of F1FO ATPase. Exposure of P. aeruginosa with A-type proanthocyanidins reduces the different proteins involved in the synthesis of ATP: hypothetical protein [NP_251171], cytochrome c [NP_251172], as well as protein subunits of acetyl-CoA fumarase [NP_253023], carboxylase [NP_254123], and aconitate hydratase [NP_249485] this can also lead to the indirect arrest of the biofilm formation [189]. Multiple polyphenols, as discussed above, can be an appropriate candidate to produce novel antimicrobials. Particularly polyphenols found in normal diets greatly regulate microbial cell physiology through various mechanisms and show growth inhibitory effects in a concentration-dependent manner. Thus, their development as a novel antimicrobial drug can play a significant role in lowering the global burden of deaths caused by bacteria.

5. Cardioprotective Effect of Polyphenols

Cardiovascular disorders [CDs] are the leading cause of morbidity throughout the world. Hypertension, smoking, a lazy lifestyle, and obesity are leading causes of coronary events, stroke, and heart attacks [229]. Hypertension has been considered the main risk factor for CDs in the world [230]. The renin-angiotensin system [RAS] has a key role in the pathogenesis of hypertension. Within the RAS angiotensin I have been transformed into angiotensin II [a vasoconstrictor] by an enzyme called angiotensin-converting enzyme [ACE]. A receptor, angiotensin type 1, mediates the action of angiotensin II. Angiotensin II increases blood pressure by water retention and vasoconstriction. The results of a study denoted that the regulation of angiotensin II through the receptor angiotensin type 1 controls various processes like migration, adhesion, and deposition of intercellular matrix and influences the chronic adaptive changes in cardiac and vascular growth. Angiotensin II also activates phospholipase A2 which controls blood pressure [231].

This is why the clinical drugs used as first-line therapy for the treatment of hypertension mainly target the activation of RAS by inhibiting the activity of ACE [232]. In several investigations, PCs from different natural sources were found to be effective in lowering the risks of coronary heart disease. Atherosclerosis is a disorder that causes inflammation in medium-sized arteries at vulnerable lesion-formation sites [233]. The major problem of atherosclerosis is that it can stay for a longer time without any major symptoms and finally may lead to various complications like myocardial infarction, and unstable angina [234]. Isoflavones extracted from soybeans have been reported to lower the risks of stroke and coronary diseases particularly in women but have no effect in men [235]. In an investigation conducted by Pala et al., 40 women were provided for 4 weeks with two hundred grams of acai pulp [a polyphenol-rich fruit] per day. The results of the study showed a massive reduction in oxidized low-density lipoprotein [Ox-LDL] and ROS and, the transition of cholesterol esters to high-density lipoprotein due to the consumption of acai pulp [236]. In another experiment, 50 patients with type-II diabetes mellitus were taking a 100mg/day of resveratrol tablet for 12 weeks. Results of the study suggested that there was a significant reduction in systolic pressure and cardio-ankle vascular index [237]. This is because resveratrol significantly extends longevity by upregulating the Sirt1 [a NAD-dependent deacetylase] involved in the regulation of cellular activities. Ox-LDL plays a key role in the development of atherosclerosis, thus

reduction in Ox-LDL through polyphenols can lower the risks of atherosclerosis. Polyphenols can prevent CDs through their anti-inflammatory, anti-platelet, and antioxidant activities in addition to their potential to increase the endothelial functions and levels of high-density lipoprotein [HDL] [238].

Catechin, resveratrol, and quercetin have been associated with mammalian targets of rapamycin [mTOR] signaling. mTOR is a phosphatidylinositol kinase-related kinase [PIKK] family player, which has a Ser/ Thr kinase domain at its C-terminal. CDs, such as those linked with cardiac hypertrophy, hypertension, and heart failure can be treated with the inhibition of mTOR. Polyphenols may assist in stabilizing atheroma plaques, which avoid vascular encroachment and enlargement as well as avoid thrombosis by inhibiting platelet aggregation. This idea is supported by a study in which red wine potentially reduces the time of platelet aggregation and bleeding. Resveratrol, found in wine polyphenol, inhibits platelet accumulation by blocking the functions of COX-1 [an enzyme known to generate the vasoconstrictor thromboxane A2] and other factors that increase the activation of platelet accumulation [239].

There is a clear crystal fact that Ox-LDL is strongly correlated with CDs. Literature suggested that resveratrol reduced the levels of Ox-LDL by chelating Cu2+ or scavenging free radicals [240]. To ensure the efficacy of resveratrol against CDs, forty Caucasian posts CDs patients experiencing coronary artery disorder. This group of individuals was administered with 10mg capsule of resveratrol regularly for three months. The results showed that resveratrol improved diastolic pressure of the left ventricle and endothelial functions, along with reduced LDL cholesterol concentration. In patients with atherosclerosis, endothelial dysfunction causes a reduction in vasorelaxation responses and may lead to the production of atheromatous plaques, which greatly influences the development of CDs. Among patients suffering from coronary artery disorder, resveratrol also provides immunity against damaging hemorheological modifications [241].

Different phytochemicals belonging to hydroxycinnamic acids and flavonoids can ameliorate an increase in blood pressure, which can also be a major cause of CDs. Consumption of foods enriched in flavan-3-ol [like legumes, nuts, tea, oranges, and cocoa] reduces cholesterol concentration and blood pressure [242]. Researchers reported that Trimethylamine N-oxide [TMAO] which is formed by colonic microbiota such as Proteus, Aerobacter, Clostridia, and Shigella during the production of L-

carnitine, and choline can also be a cause of CDs [243]. Eggs, marine fish, and red meat are great sources of TMAO as they have large quantities of lecithin, choline, and L-carnitine. The regular consumption of antioxidants, [such as polyphenols] and antimicrobial foods is known to regulate the gut microbiota, which also assists in decreasing the incidence of CDs [244].

The potential of antioxidants in the treatment of CDs has been tremendously encouraged due to their ability to lower the concentration of ROS in the vasculature and, as a result, reduce their dangerous effects [245]. Polyphenols are gaining attention to lower the global burden of CDs due to their strong antioxidant potential [246]. In the diet, the most prevalent antioxidants are polyphenols, and their consumption is 10 times greater than that of vitamin C which is water soluble, and 100 times that of vitamin E which is lipid-soluble vitamin E [230]. The cardioprotective potential of polyphenols is shown in Figure 3. The presence of hydroxylation patterns such as the 3-hydroxy group in flavanols and catechol groups is crucial for the antioxidant potential of polyphenols [247]. The catechol ring in the structure of multiple polyphenols has been associated with their antioxidant action, as shown by the ferric-reducing ability power [FRAP]. In a study, the FRAP was further increased by using a double bond or aliphatic substitution in the aliphatic group in conjugation with the catechol ring, moreover, in addition to the OH groups there was no significant increase in FRAP. Polyphenols exert their antioxidant potential in various ways. They may do this either by reducing or increasing the activity of different enzymes or by directly interacting with free radicals. ROS that can be highly toxic to DNA, lipids, and proteins, include superoxide, hypochlorous acid, and hydrogen peroxide [H2O2] which are all immediately hunted by polyphenols like catechin and quercetin. In this respect, the phenolic core can act as a buffer and collect electrons, making ROS less reactive [230]. Polyphenols may have indirect effects on cellular antioxidant systems such as superoxide dismutase's [SODs], catalase [CAT], and glutathione peroxidases [248].

Polyphenols may also lower the production of enzymes that are involved in the generation of ROS, such as nicotinamide adenine dinucleotide phosphate [NADPH] oxidase and xanthine oxidase [249]. It's worth noting that the production of ROS leads to an increase in the quantities of free metal ions. However, we can leverage the low redox potentials of flavonoids to chelate these metal ions, thus preventing the production of free radicals. This is a constructive approach that can help us

effectively manage the production of free radicals and keep our bodies safe from CDs and other ROS-associated disorders [230, 249]. In addition to all this, polyphenols can also donate their electron from the aromatic OH group to ROS thus neutralizing their effect [250]. In parallel to all this the in vivo antioxidant potential is much lower than in vitro studies, this may be due to the transformation of polyphenols into different compounds inside the body with low antioxidant potential. By blocking the OH group, metabolism lowers the polyphenol's potential to scavenge the radicles [230]. Because vitamin C, proteins, thiols, and uric acid produce an antioxidant barrier to overlook the contribution of PCs in plasma, the contribution of polyphenolic antioxidants is quite low [251]. Putting things into a nutshell, the theory that consuming foods rich in polyphenols increases the antioxidant capacity of plasma has been debunked. Other dietary components such as vitamins E and C absorbed alongside PCs, can be blamed for this increase [252].

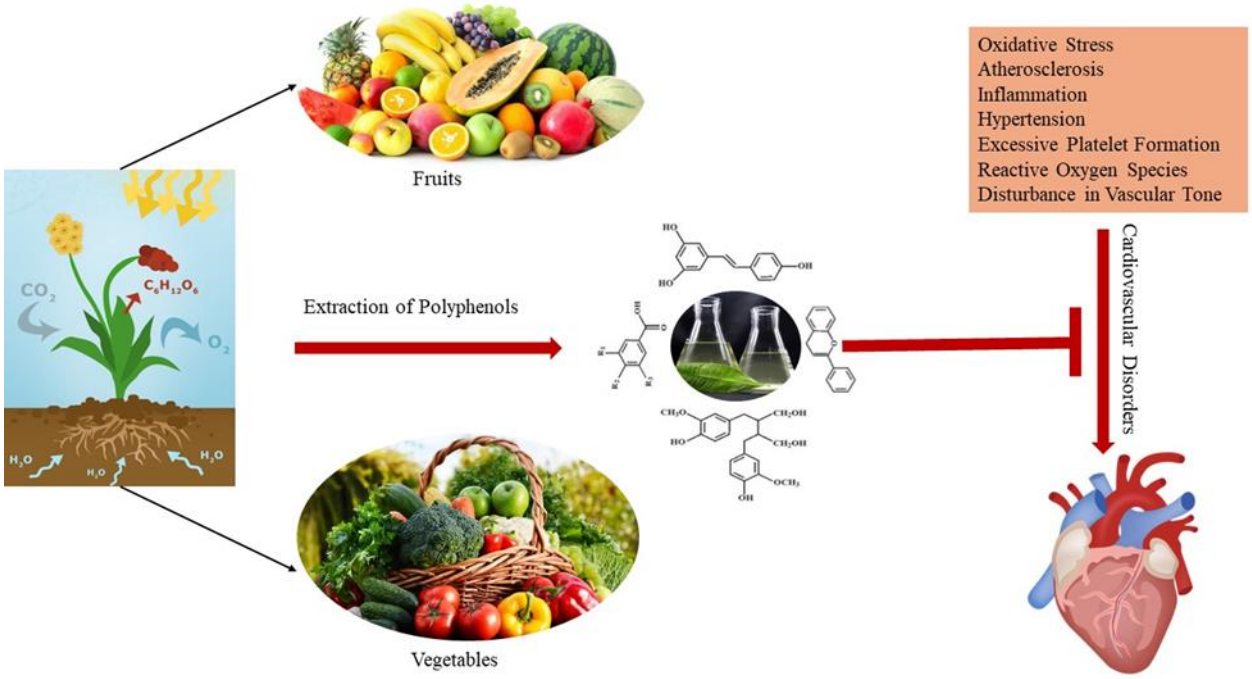


Figure 3 Cardioprotective effects of polyphenols

Nitric oxide [NO] produced by endothelium plays a significant role in controlling blood pressure and vascular tone. NO activates the cascade of G protein kinase in the smooth muscles of the artery. As a result of the activation of this cascade, the K channels get stimulated leading to hyperpolarization of the membrane and inhibiting intracellular Ca influx, which causes blood vessels to dilate. In addition, G

protein kinase lowers the contraction of blood vessels in smooth muscle in arteries by increasing the phosphorylation of myosin light chains. NO generation is principally responsible for the effect of polyphenols on the endothelium [230].

It was investigated that with ingestion of red wine PCs [RWPC] for 30 min [1 g/kg body weight] the circulating concentrations of NO reached 30 and 40 nM in adults. Uplift in the heartbeat and a reduction in blood pressure [11 mmHg] have also been observed [253]. Findings of a study have concluded that olive oil can assist hypertensive people to decrease in their blood pressure [254], whereas RWPC can result in the relaxation of arteries that are endothelium-dependent such as the rat's aorta and mesenteric artery [255]. In addition, RWPC from skin of grapes, and quercetin demonstrate antihypertensive effects. In this context, short-term intake of RWPC reduces blood pressure in normotensive rats. The observed hemodynamic effect resulted in a significant improvement in endothelium-dependent relaxation and the activation of genes responsible for producing inducible NO synthase and COX-2 within the arterial wall. This positive outcome contributes to the maintenance of agonist-induced contractility - a crucial factor for healthy cardiovascular function [256]. The greater production of NO because of exposure to polyphenols is highly associated with the Ca ion-dependent cascade, among several other factors [257].

In the endoplasmic reticulum [ER] of endothelial cells quercetin and resveratrol increase the concentration of Ca ions by opening the K gates or inhibiting the Ca ion ATPase [258]. Similarly, anthocyanin and delphinidin may increase the function of endothelial cells. The former one [anthocyanin] raises the phosphorylation of tyrosine and protein-Ca2+, which regulates eNOS. Phospholipase C and tyrosine kinases both take part in Ca2+ signaling [259]. Furthermore, another investigation reported that RWPC may increase the NO levels in endothelial cells through the redox-responsive PI3/Akt gate report [260]. In endothelial cells, PCs not only affect vasodilation through NO but also boost vasodilation through PGI2. An in vitro investigation was conducted on endothelial cells of humans treated with cocoa extract enriched in procyanidins at a dose of 2 mg/L and an in vivo investigation on procyanidins found in chocolate provided to healthy volunteers. The results of the study suggested that the ratio of cysteinyl leukotrienes [LTC4, LTD4, LTE4] to PGI2 significantly lowered by 58%, and 52%, respectively [261]. In contrast, isoflavonoids, like genistein, restrict the procoagulant activity of vascular endothelium by reducing the expressions of ET-1 [262]. The complex effects of plant polyphenols on the

balance of NO in the circulatory system may very well be responsible for their antihypertensive effects [263].

The excessive production of platelets may lead to different long-term vascular disorders. This is due to the activation of multiple adhesion proteins in the granules, which can cause several thrombotic diseases. Multiple changes occur in the body at the time of activation of platelets, one of them is the transformation of arachidonic acid to thromboxane A2 [TXA2], through the cyclooxygenase cascade. For the activation of platelets, they [platelets] bind with the collagen protein thus activating the platelets. It's well-documented that extracts enriched in polyphenols significantly inhibit the binding of platelets with collagen proteins when they are stimulated by thrombin. The anti-platelet activity of polyphenols is based on their potential to reduce the enzymes involved in the synthesis of COX, LOX, and TXA2. However, polyphenols are also antagonists of the TXA2 receptor, which indicates that flavonoids, through their suppressive effect on COX1, can reduce TXA2 concentration in the blood. In an in vivo dog model, an investigation of the effects of white and red wine and grape juice on the aggregation of platelets was conducted. The results of the investigation showed that grape juice and red wine have strong antiplatelet activity while white wine does not. Moreover, aggregation of platelets due to collagen results in increased oxidative stress which boosts the Ca concentration in the process. Flavonoids such as catechin, quercetin, and kaempferol have been shown to reduce oxidative stress by inhibiting the NADPH-oxidase [230].

6. Antiviral Properties of PCs

Viruses are acellular and cause many pathological diseases like Chickenpox, Herpes, Influenza, AIDS, Mumps, Measles, Viral Hepatitis, etc. Viruses are small particles and contain DNA or RNA genome, some of the viruses are enveloped or some of them are non-enveloped. They take over the machinery of the host and divide multiple times. Phytochemicals act through multiple targets and inhibit the replication of viruses; some of them hinder the virus attachment and entrance into the cells or inhibit DNA replication and protein translation. Some flavonoids attach themselves to the virus surface protein [264].

Here we will discuss only some of the viruses and some active PCs that can target the viruses used as strong anti-viral agents. Influenza [RNA virus] belongs to the family of Ortho-myxoviridae, and genus α-influenza virus and β-influenzavirus. EGC

[phenolic compound] is present in green tea was tested against influenza A & B. 400 µg/ml of EGC was tested against the MDCK cell line [Madin-Darby canine kidney] and inhibited the viral infection [265].

Another virus from the family Flaviviridae is named Dengue virus [single-stranded RNA virus], the well-known virus of this class transmitted through Aedes agypti and Aedes albopictus mosquitoes. Quercetin 50 µg/ml concentration for 5 hours, the DENV-2 RNA declined by more than 75.7% ± 1.57. Baicalin was effective against DENV-2 at the concentration of IC50 14.9 µg/ml, it strongly inhibited the intracellular stage of DENV-2 and targeted DENV-2 replicons Nsps [non-structural proteins] [266].

The Hepatitis C virus is a causative agent of both chronic & acute liver disease and infects 3% of the world's population. The blood-borne virus and transferred through blood, needles unsafe sexual activities. Silymarin a phenolic compound actively inhibited the hepatitis virus, when exposed to 4 hours/daily for 14 consecutive days with a dose of 5-20mg/kg, HCV replicons numbers decreased in patients and when not subjected to patient numbers again increased [267]. Similarly, in another study Shibata et al. found the same results when apigenin was exposed to HCV, it inhibited the HCV by targeting its replication process [268]. Naringenin is a flavonoid that effectively suppresses HCV secretions by 80% at 200 µM concentration [269].

HIV [retroviruses] causes AIDS which attacks the immune system of the body. It has a special enzyme Reverse transcriptase which can convert viral RNA into double-stranded DNA in the host cell. Baicalin inhibited HIV-1 by about 80% at the effective concentration of 40-400 µM [257]. Phenolics are active inhibitors of viruses belonging to a diverse range of classes e.g. Japanese encephalitis virus, Chikungunya virus, enterovirus, Poliovirus, SARS-CoV-1, cardio virus, rhinovirus, Zika virus, herpes virus, coronavirus, Ebola virus, and coxsackievirus.

7. Anti-aging benefits of PCs

Aging is a natural phenomenon leading to increased physical susceptibility, retardation of physical activities, and compromised metabolic functions resulting in higher risk of death. These factors contribute equally and can cause several disorders and multiple diseases like diabetes, obesity, osteoporosis, cancer, osteoarthritis, cognitive decline, dementia, and heart diseases, along with several neurodegenerative diseases. Recent studies revealed that epigenetic events control the process of aging. According to the literature, there are some key players, which are epigenetic changes, loss of proteostasis, genomic instability, telomere attrition,

mitochondrial dysfunction, dysregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication could lead to aging. The aging process can be slowed down by using the following strategies including mTOR inhibition, inflammation control, telomere reactivation, and the use of bioactive compounds [270].

Considering such compelling options, polyphenols have multiple targets and the potential to reduce the process of aging effectively. As mentioned above, some phenolics like curcumin, resveratrol, and quercetin have a protective role against ROS-induced damage, decrease the inflammatory response, and induce apoptosis. Moreover, polyphenols restore the activity of the antiaging protein [klotho promoter] found in renal tissue and suppress fibrosis [114]. Similarly, resveratrol was found to increase the genome stability of mouse embryonic fibroblasts, a protective shield against ARF/p53 pathway mutation [271]. In this way, the genomic and genoprotective effects exerted by polyphenols on genomic instability are evident. Sirtuin family protein Sirt-1 modulates senescence and cell lifespan, regulators of epigenetic information, generally associated with longevity. A well-studied PCs, resveratrol augments the activity of Sirt-1-mediated signaling pathways and enhances the brain health of rats [272]. Some other PCs like quercetin, naringenin, and silymarin help to invert age-related impairment, and monoaminergic neurotransmitter secretion by increasing Sirt-1, inhibiting NF-κB pathway in the hippocampus of rats, repairing cognitive functions and motor coordination [273].

8. Anti-Alzheimer's Effect of PCs

Alzheimer's is an irreversible neurodegenerative disease and a common form of dementia, related to memory deterioration and neuronal loss. It can be characterized by the presence of extracellular senile plaque in the brain area and intracellular neurofibrillary tangles of hyperphosphorylated Tau protein. Alzheimer's involves an amyloidogenic cleavage pathway through which beta-amyloid [Aβ] is produced due to action of β- and γ-secretase on the amyloid precursor protein. Aβ is the major component of senile plaque. Amyloid precursor protein [APP] is processed in two pathways either amyloid pathways or non-amyloid pathways. Flavonoids possibly display anti-Alzheimer activity, either by inhibiting β-secretase [amyloid pathway] or promoting α-secretase [non-amyloid pathway]. Self-aggregation of Aβ forms oligomers and ultimately amyloid plaques. Flavonoids could potentially exhibit the ability to inhibit the formation of amyloid plaques by

binding to Aβ, inhibiting aggregation, or promoting the formation of non-toxic off-target oligomers. Toxic Aβ monomers and oligomers might be able to induce microglial activation and proliferation. The microtubule-associated protein tau is hyper-phosphorylated in Alzheimer's, which can lead to the dissociation of tau protein from the microtubule, leading to mislocalization to the somatodendritic region. Literature shows that flavonoids hinder tau phosphorylation by modulation of the following kinases: GSK3β, CDK5, ERK2, JNK, p38, and Akt [274].

9. PCs and Parkinson's disease

Parkinson's disease [PD] is another neurodegenerative disorder and affects about 1% of the worldwide population, key features of PD are the loss of dopaminergic neurons in the nigrostriatal area and the formation of Lewy bodies that contain amyloid aggregates of misfolded a-synuclein. The major symptoms of PD are motor deficits such as tremors, bradykinesia, and muscle rigidity. Neuronal death is not clear but certain factors like environmental and genetic may contribute [274].

Lim et al. investigated the preventive effects of apigetrin on neuroinflammation induced by LPS in BV-2 microglia cell lines. Agigterin put on display neuroprotective effect by reducing the level of iNOS, prostaglandin E2, and COX-2, NF-κB and enhanced HO-1 [hempxygenase 1] and Nrf2 expressions in LPS-stimulated BV-2 cells [275]. Zhu et al. describe the neuroprotective effect of luteolin against Lipopolysaccharide-induced inflammatory and oxidative damage microglia model [276]. Luteolin reduces rotenone-induced toxicity by preventing ROS and genes related to PD, regulated mitochondrial function, mitophagy, and protein Pink1, Dj-1, and synuclein which can help to prevent cell death. Along with this rotenone-induced apoptosis, decreased Park2 and increased the Lrrk2 mRNA in Bv2 cells [277]. Several other in vitro, in-vivo, and clinical data suggested the effective role of PCs against neurodegenerative disorders.

10. Anti-rheumatoid arthritis effect of PCs

The immune system is the defense system of the body that helps to protect the body against pathogens, an imbalance in immune system homeostasis leads to severe disorder. Sometimes the body produces auto-antibodies against its body resulting in self-attack [auto-immune diseases]. Rheumatoid arthritis [RA] is among the top in the list of 100 different types of arthritis. If RA remains untreated it can lead to irreversible or permanent destruction of joints and may become a global burden in the health care system [278].

Hesperidin [HSP] is a bioactive compound that exists in citrus fruit and potentially suppresses collagen-induced arthritis. 3 mg/0.3 ml of HSP-G [a-glycosyl hesperidin] for 31 days can improve collagen-induced arthritis [279]. Xuzhu et al. showed that resveratrol 20 mg/kg suppressed IgG1 and IgG2a and reduced rheumatic symptoms [280]. In another trial, 50 mg of resveratrol on FLS in humans suppress prostaglandin E2, AKT, NADPH, COX-2, ROS, NF-KB, ERK1/2, and P38 MADK [281]. In another study, a 6.25-50 mM dose of resveratrol suppressed IL-1b, p-AKT, MMP-3, and PI3K-AKT [282]. Administration of 20-50 mg/kg dose of EGCG suppressed arthritis, in addition to this, the treated group showed less occurrence of cartilage destruction, inflammation, and CII antigen-specific IgG2a levels. 50mg/kg EGCG lowered the expressions and production of various interleukin IL-6, IL17, IL-1b, VEGF, TNF-a, nitro-tyrosine, iNOS and P-STAT3 705/727 [283]. Through multiple mechanisms, PCs perform their action against RA and contribute to lowering the challenges faced by the global health system.

11. The anti-parasitic activity of PCs

As mentioned above, PCs actively help to reduce cancer progression, anticancer, antidiabetic, antifungal, antimalarial, antibacterial, antiviral, and antiaging along with this they also act as anti-parasitic. Polyphenols and terpenoids act against protozoan parasites through several mechanisms including cell lysis, cytoplasmic condensation, phospholipid metabolism disruption, and depleting the pathogens of important lipids such as phosphatidyl glycerol [PG] and phosphatidyl inositol [PI] lipids. Phenolic exerts anti-parasitic activity against protozoan parasites mainly Leishmania amazonensis, Toxoplasma gondii, Trichomonas vaginalis, Cryptosporidium spp., Blastocystis spp., Giardia lamblia etc. [284].

Resveratrol is also present in propolis, showing anti-trichomonal activity by modulating hydrogenosome metabolism, Hydrogenosome is an organelle that produces hydrogen in anaerobic organisms, energy production, and is involved in redox balance in eukaryotes including protozoa. Resveratrol changes the expression of various proteins involved in hydrogenosome metabolism including [Fe]-hydrogenase [Tvhyd], pyruvate-ferredoxin oxidoreductase, and heat shock protein 70 [Hsp70], which can cause hydrogenosome dysfunction and inactivation of the parasites [284].

Kaempferol, another phenolic, by modulating the expression of actin, myosin II heavy chain, and cortexillin II, affects the adhesion mechanism of the parasite [285].

Epicatechin exerts the same effect as shown by kaempferol and resveratrol, modifying the expression of actin, HSP 70, and myosin II heavy chain along with energy metabolism-related enzymes like fructose-1,6-biphosphate aldolase and glyceraldehyde-phosphate dehydrogenase [286]. Quercetin, caffeic acid, and apigenin also exhibit anti-parasitic effects e.g. Apigenin-induced swelling in mitochondria, upregulated ROS, and inhibited cell proliferation in L. amazonensis [287]. Quercetin upregulated ROS, mitochondrial dysfunction, as well as membrane potential interference in L. amazonensis [288]. Caffeic acid stimulates morphological changes, the integrity of mitochondrial and cellular plasma membranes, and promotes apoptosis [289].

Future Insight

PCs are a highly effective class of secondary metabolites that exhibit a greater range of biological activities including cardioprotective, antioxidant, antitumor, antimicrobial, antidiabetic, anti-Alzheimer, antiaging, etc. In addition to all this, skin care activity of PCs extracted from the extracts of different mushrooms has also been observed. Even though there is comprehensive information regarding the biological activities of polyphenols, the clear-cut facts of PCs directly on human health remain weak. This statement is based on inaccurate measurement of PCs concentration in the analyzed drink or food, inadequate understanding of their absorption and metabolism, and a serious challenge of identifying which PC is responsible for a particular action, as multiple classes of PCs are present. Therefore, current literature strongly supports the idea that the health benefits of PCs are likely due to a combination of various phytochemicals rather than any single PC. Moreover, education and awareness are also required in public to highlight the importance of consumption of diet enriched in PCs. In addition, to enhance the bioavailability and bioactivity of PCs agricultural practices should also be modified to produce crops, fruits, or vegetables enriched in more PCs, and create certain synergistic interactions to increase their absorption when they are taken in as the most significant limitations on the use of PCs is their poor absorption. Further investigations are required to better understand the potential interactions between nutraceutical polyphenols, and medications that could impact their therapeutic efficacy.

Author Contributions

Muhammad Ishaq and Muhammad Faisal Maqbool searched the literature and wrote the book chapter, Muhammad Khan, designed and approved the final version of the book chapter, Abrar ul Haq, Hafiz Abdullah Shakir, and Muhammad Irfan, proofread, formatted, and revised the manuscript.

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Conflicts of Interest

All authors show no conflict of interest.

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