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Anticancer flavonoids producing endophytic fungi: A review

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ABSTRACT

Plants living in different environments inhabit endophytic microbes. The relationship between plants and endophytic microbes may be symbiotic or parasitic. Transmission of endophytes varies when they are obtained through roots or cracks on bark or airborne spores from soil or originated from seeds or pollens. Endophytes could be bacteria or fungi. So far, actual flavonoids have been detected from endophytic fungi only. Several flavonoids like rutin, quercetin, kaempferol, naringenin, vitexin, apigenin, luteolin, chrysin, and silymarin are isolated from endophytic fungi. These flavonoids are tested for their anticancer activity on different cell lines and their mechanisms were determined. This review focuses on endophytic fungi from which anticancer flavonoids have been reported.

1. Introduction

It has been worldwide accepted that natural compounds play a substantial role in the drug discovery and development process as a source of diverse and novel templates for new drug exploration.[1] These natural products are either produced by microbes or a result of microbial interactions with their hosts, so this domain of endophyte research for novel compounds is in a position to promote the drug discovery process to a higher level.[2,3] Endophytes are microorganisms which exist in living healthy plant tissues and do not cause any disease symptoms in their host plants.[4] However, the same organisms may also be described as saprobic or pathogenic in specific conditions like biotic or abiotic stress. Endophyte transmission may be vertical through the seeds and pollen grains or horizontal via the rhizospheric soil or airborne spores.[5–7] The route of endophyte entry varies, which can be from the cracks in the lateral root junction, wounds caused by phytopathogens,[8] root hairs and interspaces between the epidermal cells.[9,10] Endophytes mainly comprise two groups of microbes: Fungi and Bacteria. However, archaebacteria, algae, protozoa, and nematodes are rarely found to be living as endophytes.[11–13]

The plantation is preferred for phytoremediation i.e. controlling pollution pertaining to atmosphere and heavy metals present in upper layer of land. As far as combination of plants and microbes is concerned, the plants offer the habitat and nutrients to the associated endophytic microbes. In return, the associated microbes enhance the stress tolerance of the plant and/or improve plant growth and detoxify the plant environment by degradation of the pollutant. This is facilitated by phytochemicals released by plants and also those produced by microbes. Ultimately, these compounds are produced as secondary metabolites from primary ones which are consumed from host plants. Endophytes are able to produce a multitude of secondary metabolites with diverse biological activities.[14,15] For competing with co-occurring endophytes, other pathogens, and hosts, endophytes synthesize a wide range of compounds that fall into several categories like alkaloids, benzopyranones, benzoquinones, flavonoids, phenols, steroids, terpenoids, tetralones and xanthones.[16]

There are few originations of metabolite biosynthesis associated with this endophyte-host interaction-metabolites derived from endophytes due to plant interaction, metabolites derived from plants due to endophyte induction, and metabolites as results of bilaterial synthesis (Fig. 1).[17] Bacterial endophytes may strongly influence the performance, growth, and stress tolerance of plants.[18–20] In this respect, an example is the synthesis of an antimalarial compound artemisinin which is enhanced by an endophytic *Actinobacterium*, *Pseudonocardia* sp. strain YIM 63111, residing in *Artemisia annua*.[21] But no particular flavonoid compound synthesized by endophytic bacteria was identified. This induction of secondary metabolite production by endophytes is a widely spread phenomenon in medicinal and aromatic plants. In the second way, some metabolites are not only produced by a single organism but might be produced by a plant in combination with associated endophytes.

This endophytic association between microbial and autotrophic organisms in nature is ubiquitous. Complexity in endophytic relationships made researchers undertake research works that revealed their

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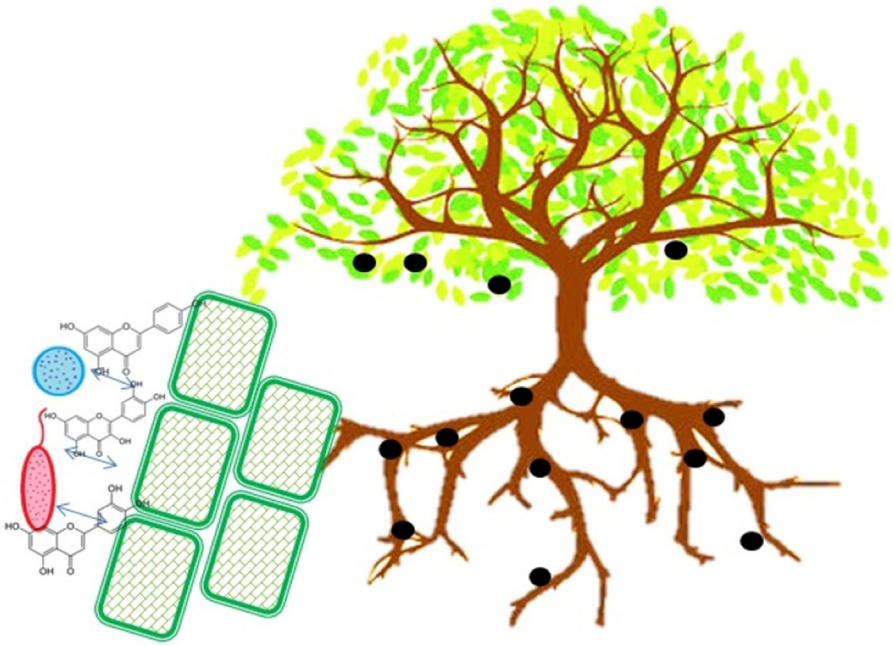


Fig. 1. Interaction of flavonoids between endophytic microbes and plant.

mechanisms and possible applications.

Till date, several flavonoids have been tested for their anticancer activity through various *in vitro* and *in vivo* models and found effective. As per etiopathology of cancer explored so far, routine mitochondrial activities result in the generation of moderate levels of reactive oxygen species (ROS) which are involved in redox signalling necessary for growth, differentiation, and cell proliferation. However, excess of ROS results in DNA mutation, protein and lipid damage, and activates pro-oncogenic signalling pathways which ultimately contribute in carcinogenesis.[22,23] The microenvironment of cancer cells has significantly higher ROS levels as compared to homeostatic conditions of non-tumor cells. This higher level of ROS could be harmful to cancer cells, leading to cell death. It is reported that, flavonoids exhibit antioxidant biological activity in non-tumor cells while pro-oxidant activity in cancer cells by inducing increased oxidative stress, thereby inhibiting cell proliferation signalling, suppressing pro-inflammatory cytokines, promoting apoptosis, necrosis, and autophagy activation.[24] The ability of flavonoids to scavenge ROS is associated with the presence of a number of phenolic hydroxyl groups in their molecular structures. This is due to hydroxyl groups facilitating intense electron exchange for substitution reactions with free radicals to form a more stable compound. Therefore, the more the number of hydroxyl groups, the higher the antioxidant and pro-oxidant capacities of flavonoids.[25] Flavonoids also inhibit cyclo-oxygenase enzymes involved in the conversion of arachidonic acid into prostaglandins which are inflammatory mediators.

In this article, we focussed on the biology and ecology of endophytic fungi associated with hosts and the types of flavonoids they produce, which have the potential to be used as anticancer agents.

2. Endophytic fungi

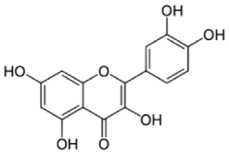
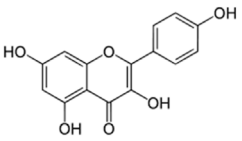
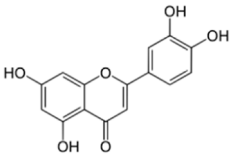
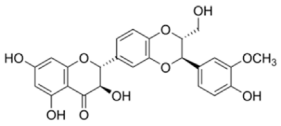
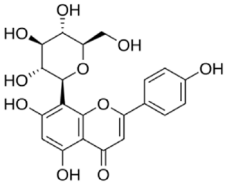
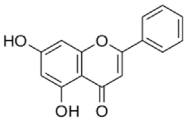
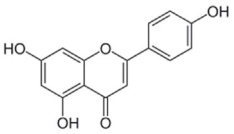
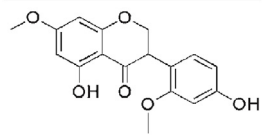
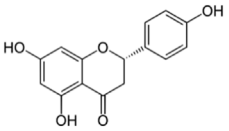
Many endophytic fungi are transmitted horizontally by the production of conidia or other spores on plants that may spread to adjacent uninfected plants and are not directly inherited through germplasm from the previous generation of the host. Therefore, with each host generation, fungi present in the external environment must compete to colonize the empty places within new hosts. Alternatively, some endophytes, grow intercellularly throughout above-ground parts of plants and are transmitted vertically via seeds. The hyphae growing into the developing seeds or vegetative parts of infected maternal host plants serve as a vehicle for the spreading of endophytic fungi. The fungal endophytes are divided into two groups. The first group comprises a large number of fungal species with a broad range of host plants, and the second group includes a smaller number of specialized fungal species that colonize some monocotyledonous hosts.[26]

Secondary metabolites of endophytic fungi have been demonstrated to strengthen the host's immune system, reducing the severity of infections and the damage caused by pathogenic microorganisms.[27] The biocontrol systems of plants are responsible for the production of various kinds of biologically active compounds, which shield plants against potentially lethal diseases and stimulate their development.[28,29] A wide array of secondary metabolites in fungi is biosynthesized from very few key precursor compounds by slight variations in basic biosynthetic pathways and can be classified into nonribosomal peptides, polyketides, alkaloids, coumarins, flavonoids, lignans, saponins, terpenes, quinones, xanthones, and miscellaneous compounds. Flavonoids are synthesized by the phenylpropanoid pathway from phenylalanine using enzymes such as phenylalanine ammonia lyase (PAL), chalcone synthase, chalcone isomerase, and flavonol reductase.[30] Table 1 summarized the flavonoids prepared by endophytes with their host plant.

3. Anticancer activity of flavonoids isolated from endophytic fungi

So far, several flavonoids have been reported to be isolated or present in endophytes. Flavonoid is the group of structurally similar compounds having phenyl benzo pyrone moiety. Different types of flavonoids include Flavanones (Naringenin), Flavones (Apigenin, Vitexin, Luteolin, Chrysin), Flavonols (Kaempferol, Silymarin, Quercetin), and Isoflavones (Cajanol). These flavonoids were tested for their anticancer activity against cell lines, for many of their mechanisms have also been deduced (Table 2). These flavonoids have been studied in detail for their action on different cancer cell lines of animal or human origin, e.g. breast, lung, cervical, prostate, leukemia, etc. Different researchers have deduced different mechanisms of action for this anticancer potential. On detailed review, flavonoids were found effective against cancer at several levels. Flavonoids do suppress pro-inflammatory cytokines like TNF-α and interleukins (extrinsic pathway involving main signaling protein-caspase

Table 1
List of flavonoids produced by endophytic fungi of host plants.

Flavonoid	Endophyte	Plant	Reference
Rutin or Quercetin 	*Xylaria* sp.	*Ginkgo biloba*	31
	Aspergillus flavus	*Aegle marmelos*	32
	Chaetomium sp.	*Nerium oleander*	33
	Nigrospora oryzae	*Loranthus micranthus*	
	Aspergillus nidulans, *Aspergillus oryzae*	*Ginkgo biloba*	34
	Annulohypoxylon squamulosum	*Cinnamomum* sp.	35
	Penicilluim commune and *Penicilluim glaucoroseum*	*Rumex nervosus*	36
	Aspergillus flavipes	*Plicaturopsis crispa*	
Kaempferol 	*Annulohypoxylon boveri* var. *microspora,*	*Cinnamomum* sp.	37
	Fusarium chlamydosporum	*Tylophora indica*	38
	Mucor fragilis	*Podophyllum hexandrum*	
Luteolin 	*Aspergillus fumigatus*	*Cajanus cajan*	39
	Penicilluim commune and *Penicilluim glaucoroseum*	*Rumex nervosus*	36
	Aspergillus flavipes	*Plicaturopsis crispa*	
	Annulohypoxylon boveri var. *microspora*	*Cinnamomum* sp.	37
Silymarin 	*Aspergillus iizukae*	*Silybum marianum*	40
Vitexin 	*Colletotrichum* sp.	*Ginkgo biloba*	41
	Dichotomopilus funicola	*Cajanus cajan*	42
Chrysin 	*Alternaria alternata,* *Colletotrichum capsici,* *Collidiotrichum taiwanense*	*Passiflora incarnata*	43
	Fusarium chlamydosporum	*Withania somnifera*	36
Apigenin 	*Chaetomium globosum*	*Cajanus cajan*	44
	Paraconiothyriu mvariabile	*Cephalotaxus harringtonia*	
	Colletotrichum sp.	*Ginkgo biloba*	45
	Aspergillus flavipes	*Plicaturopsis crispa*	36
	Fusarium chlamydosporum	*Withania somnifera*	
Cajanol 	*Hypocrealixii*	*Cajanus cajan*	46
Naringenin 	*Penicilluim commune* and *Penicilluim glaucoroseum*	*Rumex nervosus*	36
	Aspergillus flavipes	*Plicaturopsis crispa*	
	Fusarium chlamydosporum	*Withania somnifera*	

8) and downregulate Bcl-2 and Bcl-xL, and upregulate Bax (intrinsic pathway activating caspases 9). Both these events bring out the activation of caspase 3, 6, and 7, ultimately resulting in the apoptosis of cancer cells.[47] As stated earlier, flavonoids also act as pro-oxidants. This ability results from suppression of cancer cell proliferation by inhibition of epidermal growth factor receptor/mitogen-activated protein kinase (EGFR/MAPK), phosphatidylinositide 3-kinases (PI3K), protein kinase B (Akt) as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).[48]

In the entire progression of cancer, chronic inflammation also plays a major role by modulating cellular transformation, survival, proliferation, invasion, metastasis, and angiogenesis pathways.[182] Flavonoids were

Table 2
Flavonoids isolated from endophytic fungi and their mechanism of anticancer activity.

Flavonoid	Type of cancer	Mechanism	Reference
Chrysin	Breast	Anti-proliferative effect	49
		↓ Cyclin D1 and hTERT	50
		EGFR ↓ and apoptosis	51
		↓ Angiogenesis, alleviation of VEGF expression and metastatic growth	52
		Inhibition of HDAC8 enzymatic activity	53
		Modulation of phase I and II enzymes	54
	Gastric	Altered microRNAs expression	55
		↓ AP-1 and suppression of early growth response-1	56
	Prostate	↓ HIF-1α	57
		↓ DNA methyltransferases	58
	Cervical	Apoptosis	59
		↑ NF-kB/p65	60
	Hepatocellular carcinoma	↑ Hexokinase-2	61
		↑ NF-kB/p65	62
		↓ Canonical Wnt and NF-κB,	63
	Skin	↓ MSK1/histone H3 signaling	64
		Neoplastic transformation by targeting CDK2 and CDK4	65
	Lung	↓ IL-6-induced AKR1C1/1C2 overexpression	66
	Leukemia	↑ Macrophage phagocytosis	67
		↑ Apoptosis in Bcl-2 overexpressing	68
		↓ SCF/c-Kit signaling	69
Luteolin	Breast	PLK-1 mediated anticancer activity	70
		↓ MMP9, ↓ AKT/mTOR-inducing H3K27Ac and H3K56Ac	71
		↑ miR-203 and ↓ Ras/Raf/MEK/ERK signaling.	72
		↓ VEGF production and KDR-mediated activity	73
	Lung	↓ Focal adhesion kinase and ↓ nonreceptor kinase signaling pathway	74
		Cell cycle arrest in G2 phase	75
		Caspase activation induced by Poly(dA:dT), and cleavage of IL-1β	76
	Colon	↓ Notch1 and TGF-β pathways	77
		↓ NLRP3/IL-1 β signal axis	78
		↓ PI3K/Akt and ERK1/2 and reduction in OGF-1R signaling	79
		↑ Glutathione-S-transferase, ↑ Nrf2, activation of GST-α and GST-μ.	80
		↓ HMGB1-TLR-NF-κB signaling pathway protein	81
	Prostate	↓ Angiogenesis mediated by Vascular Endothelial Growth Factor Receptor 2	82
		↑ Cell-cell adhesion by E-cadherin through AKT/mdm2 pathway	83
		↓ Wnt signaling by ↑ FZD6 and ↓ stemness of cancer cells	84
		↑ miR-630 and ↓ cyclin G-associated kinase	85
Apigenin	Breast	↓ p-JAK1, p-JAK2 and p-STAT3; ↑ cleaved caspase-8, cleaved caspase-3 and PARP cleavage	86
		↑ Caspase3 levels, PARP cleavage and Bax/Bcl-2 ratios	87
		↓ IFN-γ-induced PD-L1 expression and STAT1	88
		↓ p-JAK2 and p-STAT3 expression; VEGF inhibition	89
	Lung	↓ GLUT1	90
		↓ PI3K/Akt signaling pathway	91
	Prostate	Decrease in cyclin D1, D2 and E; upregulation of WAF1/p21	92
		↑ E-cadherin; ↓ in snail and vimentin	93
		↑ IκBα but no IKK activation	94
		↓ Smad2/3 and Src/FAK/Akt pathways	95
		↓ p21 and p27; ↑ caspases-8, -3 and TNF-α; ↓ PI3K/Akt and NF-κB signaling	96
	Ovarian	↓ FAK expression	97
		↓ Gli1 and ↓ CK2α	98
	Cervical	↓ CK2α expression	99
	Leukemia	↑ Caspase-9 and caspase-3	100
		↓ JAK/STAT pathway	101
		↑ JNK; Inactivation of Akt; and ↓ Mcl-1 and Bcl-2	102
	Melanoma	↑ Cleaved caspase-3 and cleaved PARP; ↓ ERK1/2 proteins, p-AKT and p-mTOR	103
		↓ FAK/ERK1/2 phosphorylation	104
	Pancreatic	Ikaros expression balancing	105
Naringenin	Breast	↓TGF-β1 secretion, ↓ PKC activity and inhibits the secretion of TGF-β1 from the trans-Golgi network, resulting in a decrease in the secretion of TGF-β1	106
		Production of reactive oxygen species (ROS), cell membrane damage, DNA damage, ↑ caspase-3/7, the cell cycle arrest	107
		Promotion of MDA-MB-231 cell movement by inhibiting the protein expression of integrin β3, MMP-2, and MMP-9,	108
	Liver	↓ Proliferating cell nuclear antigen (PCNA) and Bcl-2 and aided the Bax and caspase-3 expression	109
		↓ Propagation of HepG2 cells by G0/G1 and G2/M cell cycle arrest, and enhancement of ratio of Bax/Bcl-2, a consequent discharge of cytochrome C, and ↑ caspase-3	110
		↓ PI3K/Akt/mTOR cascade by initiating autophagy with activation of MAPKs	111
		Control of apoB secretion and cellular cholesterol homeostasis; Decrease in esterification of cholesterol, and lowered the ACAT2 mRNA; ↓ microsomal triglyceride transfer protein (MTP)	112
		↓ 2,3,7,8-Tetrachlorodibenzo- p-dioxin (TCDD)-induced CYP1A1 mRNA level and CYP1A1 gene expression in Hepa-1c1c7 cells	113
	Lung	Cell cycle arrest at G0/G1 phase. ↓ Cyclins A and D1 and phosphor-pRb while supporting CDK inhibitors like p21, p27, p53, Fas (extrinsic death receptor), and FasL. ↓ PI3K/Akt signaling pathway and ↑ cleavage of caspase-3, caspase-8, and poly ADP-ribose polymerase (PARP)	114
		↓ Matrix metalloproteinase (MMP)-2 and urokinase-type plasminogen activator (u-PA); ↑ NF-κB and AP-1 and ↓ phosphorylation of extracellular signal-regulated kinase ½ (ERK 1/2) and p38 (MAPK)	115
	Prostate	↓ Various STAT3-regulated gene products including BCL-2, BCL-xL, COX-2, cyclin D1, cyclin E, IAP-1/2, survivin, and MMP-9 VEGF, which resulted in overexpression of apoptotic proteins (p53 and	116

(continued on next page)

Table 2 (*continued*)

Flavonoid	Type of cancer	Mechanism	Reference
		p21) and sub G1 arrest and caspase-3-induced PARP cleavage.	
	Pancreas	↓ EMT markers at mRNA and protein levels by obstructing the TGF-β1/Smad3 signal process	117
	Cervix	↓ Phosphorylated (p) NF-κB p65 subunit, cysteinyl aspartate proteinase-1 (caspase-1), and cyclo-oxygenase-2 (COX-2), ↓ NF-κB/COX-2-caspase-1 pathway, inhibiting growth and causes apoptosis	118
		Intra-nucleosomal DNA fragmentation. Effect on expression of caspases, p53 and Bax, Fas death receptor, and its adaptor protein FADD.	119
		Activation of p38/MAPK causing the pro-apoptotic caspase-3 activation cleavage of poly (ADP-ribose) polymerase	120
	Brain	↓ Expression of COX-2 and iNOS due to ↑ SOCS-3 by PKCδ and AMPKα signaling ways	121
		↓ Cyclin D1, CDK 4, protein kinase C, and nuclear factor κB.	122
	Skin	↓ Bcl-2/Bax ratio and ↑ caspase-3, caspase-9, and Cx43.	123
		↓ MMP-1 and AP-1 induced by UVB and phosphorylation of Fos-related antigen (FRA)-1 at Ser265.	124
		↓ UVB irradiation- induced FRA-1 protein stability and mitogen-activated protein kinase (MEK) inhibitor.	
		↓ ERK2, which lowered UVB-triggered p90 (RSK) phosphorylation by attaching it with ATP competitively.	
		↓ Activity of ERK2 and reducing the stability of FRA1, followed by ↓ MMP-1 expression and AP-1 transactivation	
		↑ subG0/G1, S, and M/G2 period cell with a substantial reduction in G0/G1 stages	125
	Colon	Reduction in expression of cyclin D1 by increase in cyclin D1 phosphorylation	126
	Bladder	↓ MMP-2 and reduction of TSGH-8301 cell migration.	127
		↓ Translocation of nuclear factor κ-light-chain-enhancer of active B cells	
Kaempferol	Breast	↓ Expression of IRS-1 and cyclin D1	128
		↓ AHR dependent transcription	129
		ERK signaling pathway	130
		↓ MAPK signaling pathway	131
		↓ ROS-PAD4 pathway	132
		↑ DNA Damage and apoptosis	133
	Bladder	↑ Caspase-3	134
		Ubiquitin–proteasome pathway	135
		Activating p53 signal pathway	136
	Cervical	AMP-activated protein kinase-dependent autophagy	137
	Colon	↑ MMP28 and ↓ NTRK3	138
		Apoptosis and ↓ Akt activity	139
		↓ Jak/Stat3 signaling pathway	140
	Endometrial	↓ mTOR/PI3K/Akt signalling pathway	141
		↓ ER-α and the anti-apoptotic proteins	142
	Liver	↑ ER stress- CHOP pathway	143
		↓ Downregulatory action of TNF-α	144
		↓ HIF-1 and MAPK	145
		↑ Mitochondrial signaling pathways and ↓ PI3K/mTOR/MMP signalling	146
		↑ ABCA1 mRNA expression	147
	Lung	PI3K/AKT and ERK pathways in cell apoptosis	148
		↓ Unique inhibitor of the NF-κB pathway	149
		↑ MEK-MAPK signaling pathway	150
	Ovarian	↑ Autophagy mechanism	151
		↓ HIF-1α; repression of AKT phosphorylation	152
		↑ Apoptotic proteins and STAT3 signaling pathways	153
	Pancreas	↑ ROS dependent apoptosis via Akt/mTOR signaling	154
		↓ EGFR and AKT pathways	155
	Prostate	↓ Cell proliferation via androgen dependent pathway	156
		↑ PLC, PKC, and MEK1/2 cascade	157
	Skin	↓ RSK2 and MSK1 kinase activities	158
		↓ Mitochondrial pathway of apoptosis	159
		↓ PI3K activity	160
		↑ Apoptosis and ↓ mTOR/PI3K/AKT pathway	161
Vitexin	Breast	↑ Bax and ↓ Bcl-2 and caspase activity	162
	Liver	Cytotoxic effects by inducing apoptosis and inhibiting autophagy	163
	Colorectal	Cleaved poly(ADP-ribose) polymerase, cleaved caspase-3, ↑ Bax, and ↓ Bcl-2	164
	Oral	Cause antimetastatic and apoptotic effects through a p53-dependent pathway	165
	Esophagus	Inhibitory effects on cell growth, cell proliferation, and apoptosis of esophageal cancer	166
	Blood	Potently induce programmed cell death of leukemia cells as well as morphological changes in cells	167
	Ovary, cervix, and prostate	Inducing apoptosis via cleavage of PARP, ↑ Bax, and ↓ Bcl-2	168
Sylimarin	Breast	↓ Invasion, ↓ Migration, ↓ Cell proliferation, ↓ Inflammasome activation	169
	Colon	↑ Necrosis, ↓ Cell viability, ↑ Apoptosis, ↑ Autophagy	170
	Oral	↓ Cell proliferation, ↓ Tumor growth, ↑ Apoptosis,	171
	Cervical	↓ Invasion, ↓ Cell viability, ↑ Apoptosis, ↓ Migration	172
	Skin	Tumor regression, ↓ Tumor growth, ↑ Apoptosis	173
	Lung	↓ Tumor growth, ↑ Apoptosis, ↑ $CD8^+$ T-cells, ↓ IL-10, ↑ IL-2 and IFN-γ	174
	Melanoma	↓ Cell viability, ↓ Tumor growth, Cell cycle arrest, ↓ Angiogenesis, ↑ Apoptosis,	175
Quercetin	Breast	↓ Akt/PKB phosphorylation, ↓ cell proliferation	176
	Colon	↑ Wnt/β-catenin, ↓ cyclin D1, ↓ survivin	177
	Oral	↓ Hsp70 expression, changes in EMT, ↑apoptosis in drug-resistant cells	178
	Cervical	↓ Cancer cells growth, ↓ IL-6, ↓ Rb phosphorylation, ↓ cyclin D1, ↓ cell migration	179
	Prostate	↓ Cell viability, ↑ apoptosis, cell cycle arrest in G1 phase ↓ cell migration	180
	Melanoma	↓ Proliferation, ↓ cell viability, ↑ apoptosis	181

Note: Sign ↓ means downregulation, inhibition, blocking or suppression while ↑ means activation, upregulation, activation or promotion.

shown to exert anti-inflammatory action via suppression of chemokines, COX-2, cytokines, and pro-inflammatory transcription factors, inhibition of PI3K/Akt, and inhibition of kappa kinase/c-Jun amino-terminal kinases (IKK/JNK).[183]

To support the findings of anticancer activity of flavonoids, molecular docking study, drug-likeness prediction, ADMET prediction, molecular dynamics (MD) simulation study, and binding free energy calculations were performed. Molecular docking revealed the potential flavonoids having a good binding affinity with protein/enzyme or receptor. Functional groups like methyl and ketone of flavonoids form hydrogen bonds with particular amino acids located at the active site pocket formed by the folding of proteins. After molecular docking, it has been reported that many flavonoids showed a negative value of binding affinity (kcal/mol). Software-based drug-likeness prediction revealed that many flavonoids follow Lipinski's rule of five with a minimum or zero violation in the rule pertaining to molecular weight (MW), lipophilicity (mLog P), number of HB acceptors (nHBA), number of hydrogen bond donors (nHBD), and molar refractivity (MR). Pharmacophore modeling showed the standard pharmacophoric features in flavonoids. An MD simulation study provided real-time confirmation of the stability of the protein−ligand complex over the simulated time scale.[184]

As the cancer progression is a complex biochemical process, it involves numerous proteins in the form of enzymes and/or receptors. Inhibition of some of these enzymes and/or blocking of receptors thereby exerts an anticancer effect. So far, many flavonoids have been studied *in silico* by molecular docking against various targets of cancer progression. Biophysical binding and its energetics were studied thoroughly. Inhibition of antiapoptotic Bcl-2 and Bcl-xl proteins is the key target to induce the apoptosis process in ovarian cancer cells. Docking results for apigenin against Bcl-2 (PDB code: 4IEH) and Bcl-xl (PDB code: 3ZK6) proteins showed binding with Arg-105 and Phe-63 of Bcl-2 and Arg-139, Phe-105, and Ala-104 of Bcl-xl.[185] Suhail et al., 2023 studied the molecular docking of kaempferol, luteolin, and quercetin against the cancer target phosphatidylinositol 3-kinase (PI3K) (PDB code: 3L54). It showed that these flavonoids inhibit PI3Kγ (3L54) by binding with its amino acids, Ser-806, Trp-812, Ile-831, Tyr-867, Val-882, Met-953, Phe-961, Ile-963, and Asp-964.[186] Recently, Rathi et al., 2024 carried out docking of naringenin against PIM-1 (PDB code: 1XWS). It has a significant role in cell cycle progression and death in prostate cancer tissues. Docking study showed its binding with Phe-49, Val-52, Glu-89, Leu-120, Val-126, Gln-127, Phe-130, Lys-169, Glu-171, and Asp-186 of PIM-1.[187]

4. Conclusion

The relationship of plants and their inhabited fungi can be parasitic or symbiotic. The commonly found endophytic fungi are *Penicillium, Aspergillus*, and *Fusarium* species. Endophytic fungi synthesize various types of secondary metabolites, one of which is flavonoids. Reported flavonoids were rutin, quercetin, chrysin, kaempferol, apigenin, naringenin, silymarin, vitexin, etc. These flavonoids exhibit anticancer activities on different types of cell lines via different mechanisms like inhibition of JAK/STAT pathway, cell cycle arrest, caspase activation, suppression of TGF-β1 secretion, and many others. This review provided a reference for the further exploration of anticancer agents originated from endophytic fungi.

CRediT authorship contribution statement

Kirti G. Sahu: Conceptualization. **Deepak S. Khobragade:** Resources, Data curation. **Shriniwas P. Patil:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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