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Natural Flavonoids as Anticancer Agents: Targeting the HIF-1α Signaling Pathway

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Abstract

Background: The clinical effectiveness of wide range of currently available anticancer drugs is being reduced .HIF-1 alpha is essential for the reprogramming of cancer cells' metabolism,so cancer treatments include inhibiting the HIF-1α signaling pathway and The evidence underscores the potential of natural flavonoids as HIF-1α inhibitors in cancer therapy.
Objective: To provide more comprehensive overview of inhibition of flavonoids on HIF-1 which may be useful for developing new compounds with enhanced anticancer properties and also to provide reasearchers with a thought to design potent and low toxic anticancer candidates.
Material and methods: A comprehensive review of recent literature was conducted to identify studies investigating the effects of natural flavonoids and their derivatives on HIF-1α activity. Emphasis was placed on mechanisms of action, efficacy, and toxicity profiles, as well as their impact on tumor hypoxia and associated pathways such as vascularization and glycolysis.
Result: Recent findings demonstrate that various natural flavonoids effectively downregulate HIF-1α through distinct mechanisms. These compounds exhibit significant anti-cancer properties while maintaining low toxicity, making them viable candidates for further development. Several studies have also highlighted the ability of flavonoids to influence tumor vascularization and glycolytic pathways, thereby enhancing their therapeutic potential.
Conclusion: In this review in order to increase bioavailability , solubility and to better understand the impact of anticancer flavonoids on HIF-1 alpha, amino acids or amino groups were added to the flavonoid structure. understanding the effect of anticancer flavonoids on HIF-1 α may be relevant in the development of novel compounds with increased anticancer activity.

Keywords Tumor hypoxia, HIF-1α, Natural flavonoids, signaling pathway, Glycolysis, Vascularization

1. Introduction

Cancer is a medical condition characterized by uncontrolled cell growth that can spread to other parts of the body. These cells can proliferate widely, forming a lump or mass, and are considered a type of neoplasm or tumor[1]. Cancer is considered one of the most serious health conditions and the most prevalent cause of death worldwide[2]. responsible for roughly 1 in every 6 fatalities and impacting nearly every family. In

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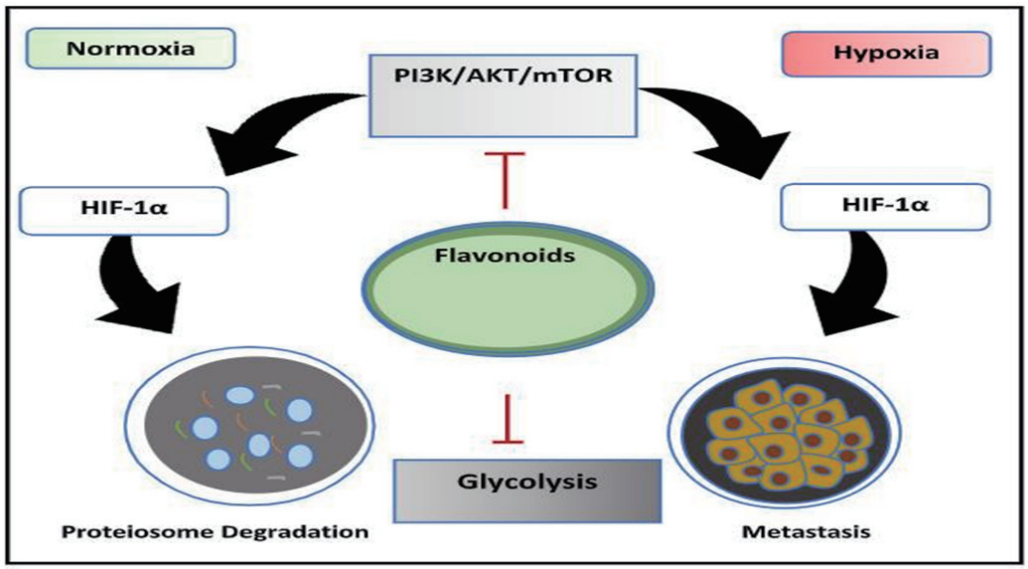


Figure 1: Graphical Abstract of Unlocking Nature's Power: Natural Flavonoids as Pioneering HIF-1α Inhibitors for Cancer Therapy

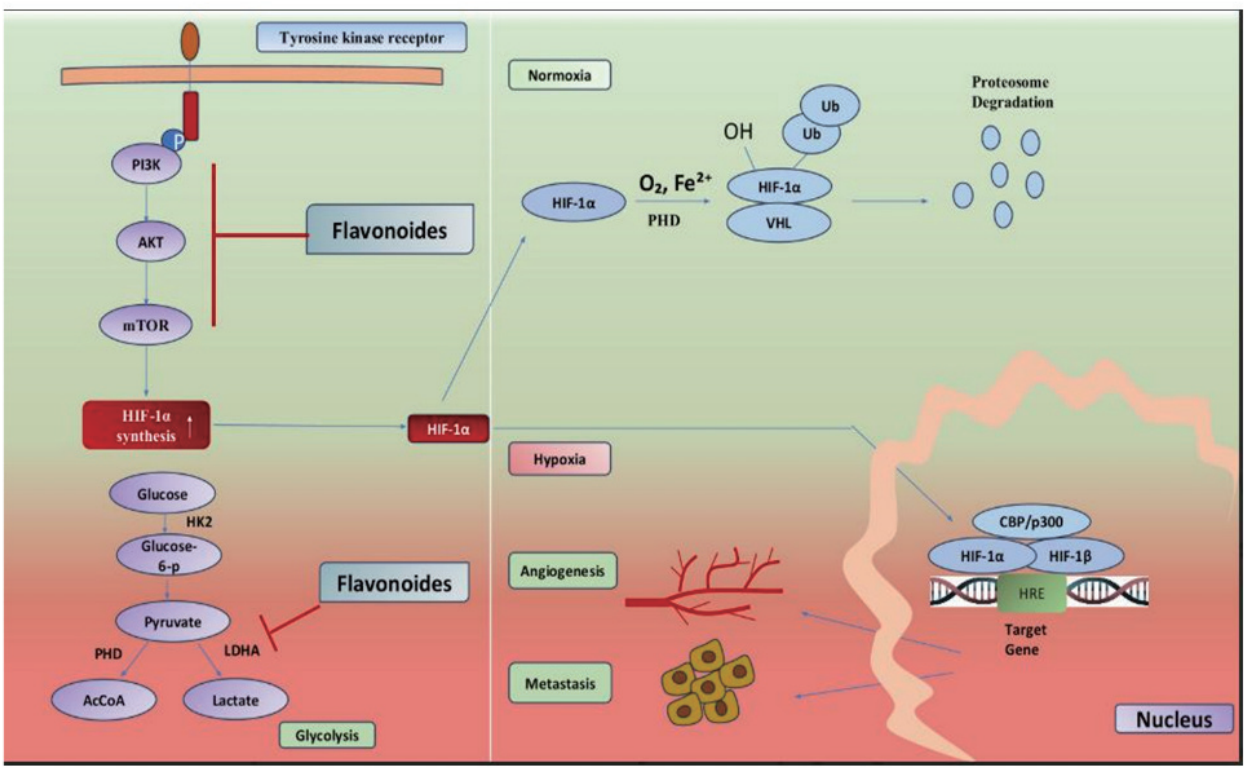


Figure 2: Graphical Abstract of Unlocking Nature's Power: Natural Flavonoids as Pioneering HIF-1α Inhibitors for Cancer Therapy

2022, there were approximately 20 million new cancer cases and 9.7 million cancer-related deaths globally. The cancer burden is expected to rise by around 76.6% by 2050, placing additional pressure on healthcare systems, individuals, and communities[3].

In spite of numerous evolutionary changes have been made to cancer treatment from surgery, Chemotherapy and radiotherapy to significant advances including stem cell therapy, targeted therapy, nanoparticles, sonodynamic therapy etc., treating cancer remains a challenge[4-7].

Flavonoids, a group of polyphenolic compounds is a typical food item for humans[8,9] The high concentration of polyphenols is found in fruits and

vegetables[10]. These compounds have been suggested as major chemopreventive agents primarily because of their capacity to selectively block the proliferation of tumor cells by blocking signal transduction, as well as their antioxidant and antimetastatic qualities through preventing tumor [11-13] term "chemopreventive" refers to a pharmaceutical strategy that aims to stop the progression of cancer before invasion and metastasis take place[14].

The ability of tumor blood vessels and glycolysis to supply oxygen and nutrients is necessary for rapid tumor growth[15]. One feature that many solid tumors have in common is tumor hypoxia, which results from the tumor's development exceeding the concurrent angiogenesis[16].

Hypoxia inducible factor 1 (HIF1) is a transcription factor that contributes to the regulation of hypoxia-associated genes and genetic changes that inactivate tumor suppressor genes and activate oncogenes. It essential for tumor cells acclimate in [17-19] have an impact on HIF-1α via various mechanisms such as HIF-1α Transcriptional activity, HIF-1α degradation, HIF-1α mRNA translation and HIF-1α Dimerization. The impact of flavonoids on the regulatory cascade of regulation linked with glucose metabolism and HIF-1 activity represents an effective approach to prevent metabolic reprogramming by controlling HIF-1 activity, by directly upregulated the expression of glycolysis

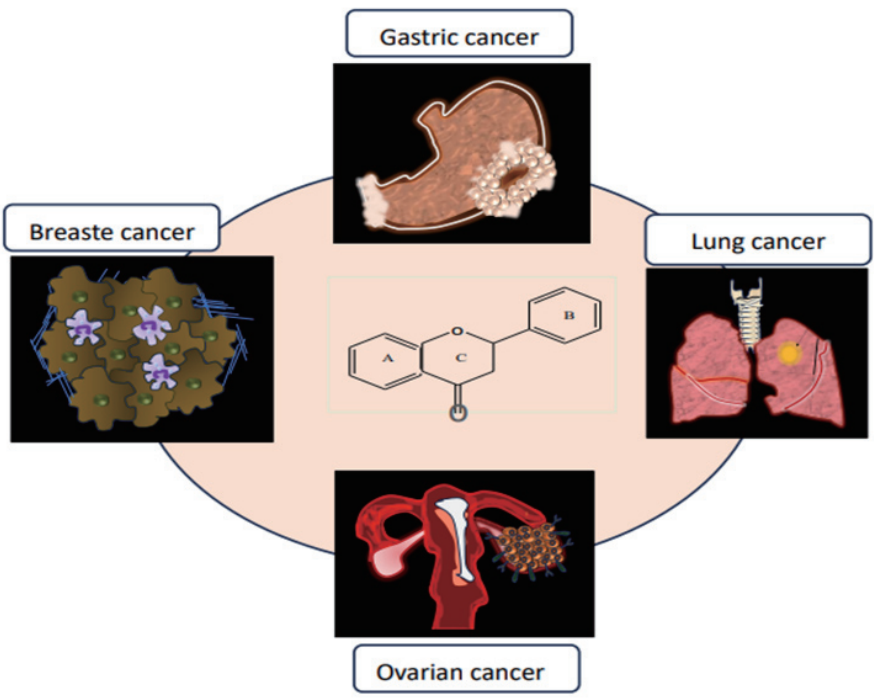


Figure 3: Use of flavonoids in various types of cancer

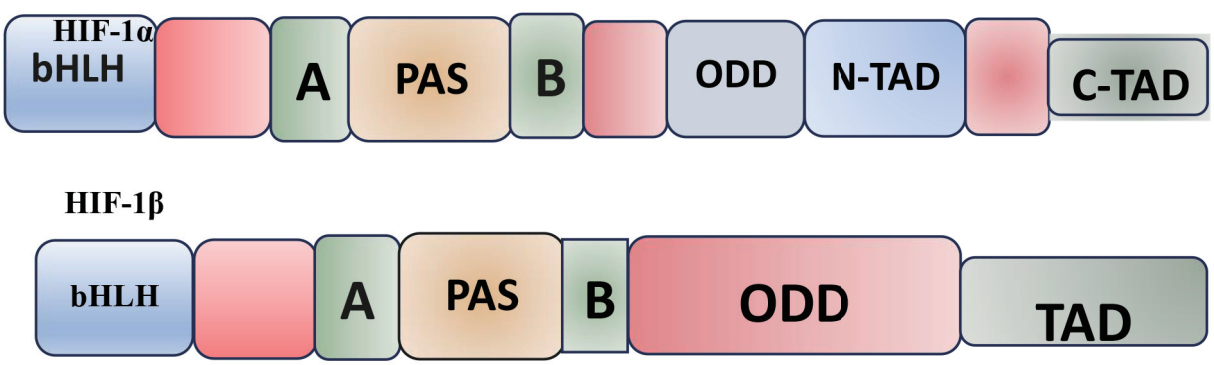


Figure 4: Structure of HIF-1α and HIF-1β subunits. Functional domains of HIF-1. bHLH: basic helix-loop-helix domain; PAS: Per/ARNT/Sim domain; ODD: Oxygen dependent degradation domain; N-TAD: N- terminal transactivation domain; C-TAD: C-terminal transactivation domain.

related transporters and important enzymes like GLUT, PFK, LDH, HK, etc. a crucial step in [11,20].

2. Structure of HIF-1α and HIF-1β Subunit

HIF-1α plays a crucial role in cancer progression and can be targeted for treatment [21,22] In 1995, Wang used DNA affinity chromatography to identify HIF-1[23]. HIF-1α is a DNA-binding complex protein [24] composed of HIF-1β and HIF-1α subunits, is one of three HIF-α isoforms, with HIF-2α and HIF-3α[25], [26] HIF-1β subunits are particularly generated in normoxic circumstances, but α subunit rapidly degrades. HIF-1α stabilized and activated hypoxia-inducible genes like ,vascular endothelial growth factor (VEGF) , under hypoxic conditions[27] .

Dimerization of both of them HIF-1α and β subunits is made possible by helix loop helix domain (bHLH). To maintain the heterodimerization of the α and β subunits, per-ARNT-sim(PAS) domains are a component of both subunit. One of characteristics of α subunit is the oxygen dependent degradation(ODD) domain. This domain is hydroxylate through prolyl hydroxylase-2(PHD2) and causing the α subunit to be degraded by proteases in normoxic [28,29] Hypoxia reduces PHD activity and increases the half-life of HIFα[30,31] N-TAD and c-TAD each , are two transactivation domains[32], these domains maintain the connection between the target gene specificity-granting HIF transcription factor and other co-activators of gene transcription, like p300/CBP[33].

3. Regulation of HIF-1α under normoxic and hypoxic condition

The proline residue of HIF-1α is hydroxylated in normoxic condition, which accelerate HIF-1α breakdown. the tumor suppressor protein Von Hipel Lindau (VHL) Facilitates HIF-1α hydroxylation and destroy HIF-1α in its ubiquinated form. Hypoxia causes a decrease in process of hydroxylation and ubiquination, which causes HIF-1α to accumulate rapidly[34,35]. A HIF-1 transcription factor is created when HIF-1α reaches the nucleus and dimerizes with HIF-1β. To start gene transcription , HIF -1 binds to hypoxia response elements (HRE),inside the nucleus[36-38] The process by which pre-exhausting vasculature gives rise to new blood cells is known as [39,40] In solid tumors, this occurs when angiogenic switch is activated in hypoxic conditions. The expression of genes controlling angiogenesis, metabolism, and cell survival, is triggered by each of the three isomers of HIF[41].

Additionally, growth hormones and oncogenic signaling have the ability to activate HIF -1α in normoxia[42]. Major signal transduction pathways, such as MAPK[43], which phosphorylates HIF-1α to promote its nuclear deposition and transcriptional activity, and PI3K/AKT pathway[44], are responsible for the non-hypoxic activation of HIF-1α[45,46] It was recently shown that treatment with CoCl2 promoted HIF-1α expression by binding to the PAS domain, which blocked HIF-1α VHL conjugation and thus stabilized HIF-1α[47]. IGF-1 stimulates the accumulation of HIF-1α subunits[48]. The regulation of HIF-1 involves numerous signaling channels [49].

4. Flavonoides

Flavonoids are the primary group of naturally occurring polyphenolic compounds[50,51] Flavonoids have a varied range of pharmacological activities[52]. The components of flavonoids are condensed aromatic ring A, heterocyclic ring C, and second aromatic ring B. The structure is referred to as the "skeleton of flavonoid diphenyl propane." Flavonoids are distinguished by the hydroxylation and conjugation patterns of the B ring, as well as the conjugation structures of hydroxyls on the A and C rings, and can be classified into six types: flavanols, flavanones, flavones, isoflavones, flavonols, and anthocyanadins. The two types of flavonoids are anthoxanthins and anthocyanins . Several different anticancer effect of flavonoids have been demonstrated [53-55].

4.1 Anthoxanthin

Anthocyanins and Anthoxanthins are the two subclasses of flavonoids. The molecules known as anthoxanthins, consist of flavonols, flavanols, isoflavones, and flavanones[56].

Originally, Baicalein(BE) was extracted from the Scutellaria baicalensis[57]. It prevented HIF-1 transcriptional activation and HIF-1α protein accumulation brought on by hypoxia. Subsequently, reasearcher demonstrated BE inhibits ROS and the PI 3-kinase/Akt pathway in BV2 microglia, which decreases hypoxia-induced HIF-1α protein and activation as well as the production of hypoxia sensitive genes[58]. The natural substance Apigenin inhibited HIF-1α's ability to bind to Hsp90, lowering HIF-1α levels. Under normal oxygen conditions, apigenin can suppress the production of HIF-1 and VEGF in ovarian cancer cells[59]. Apigenin may work

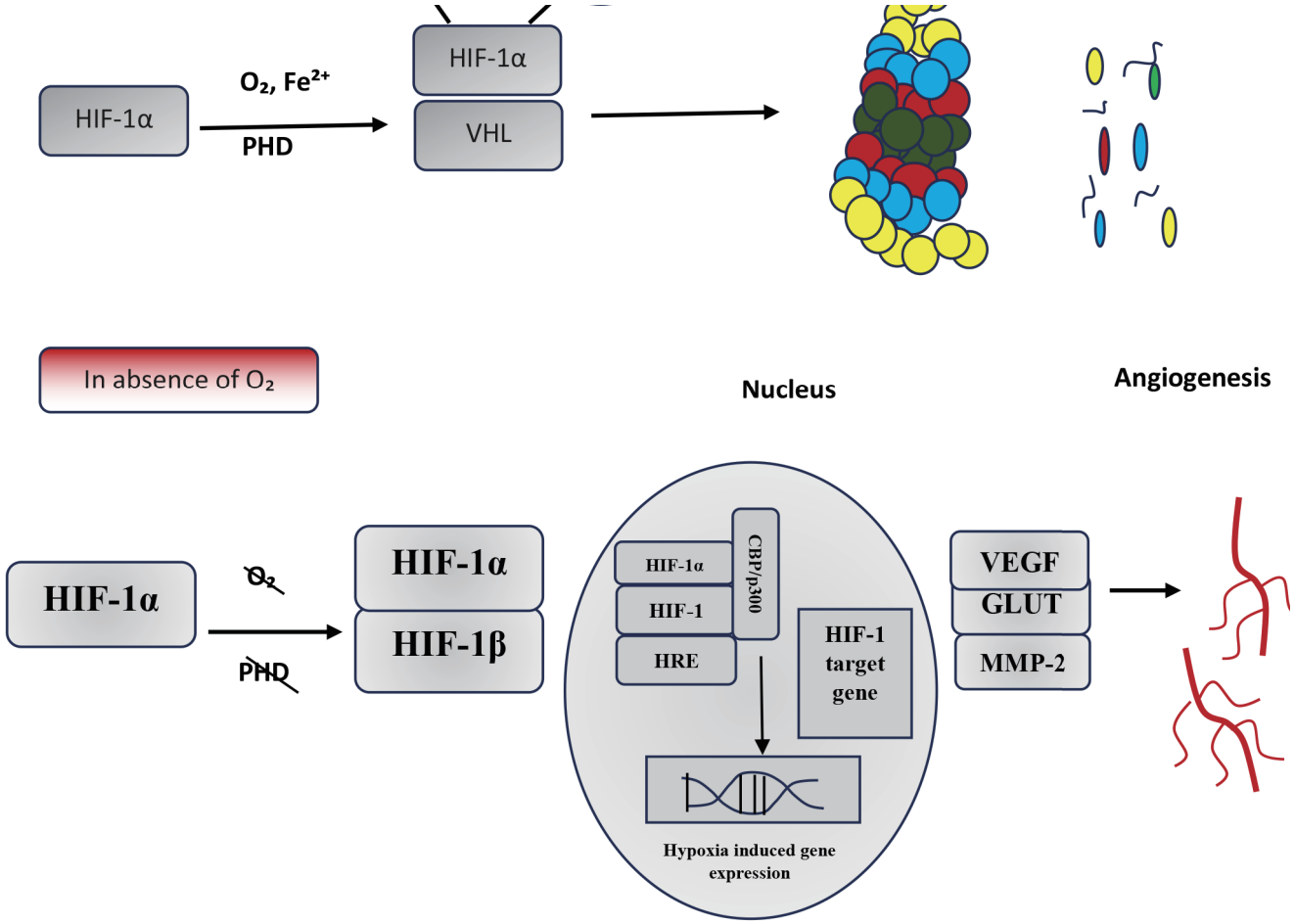


Figure 5: Regulation of HIF-1α under normoxia and hypoxia situation. In normoxia : Under normal oxygen levels, PHD hydroxylates HIF-1α, which then forms a complex with the VHL protein. The complex recruits ubiquitin ligases, which target HIF-1α for proteosomal destruction. In hypoxia: Under hypoxia, PHD and HIF are inactive. Non-hydroxylated HIF-1α is stable and can dimerize with HIF-1β. The HIF heterodimer interacts with p300/CBP to trigger the transcription of HIF target genes.

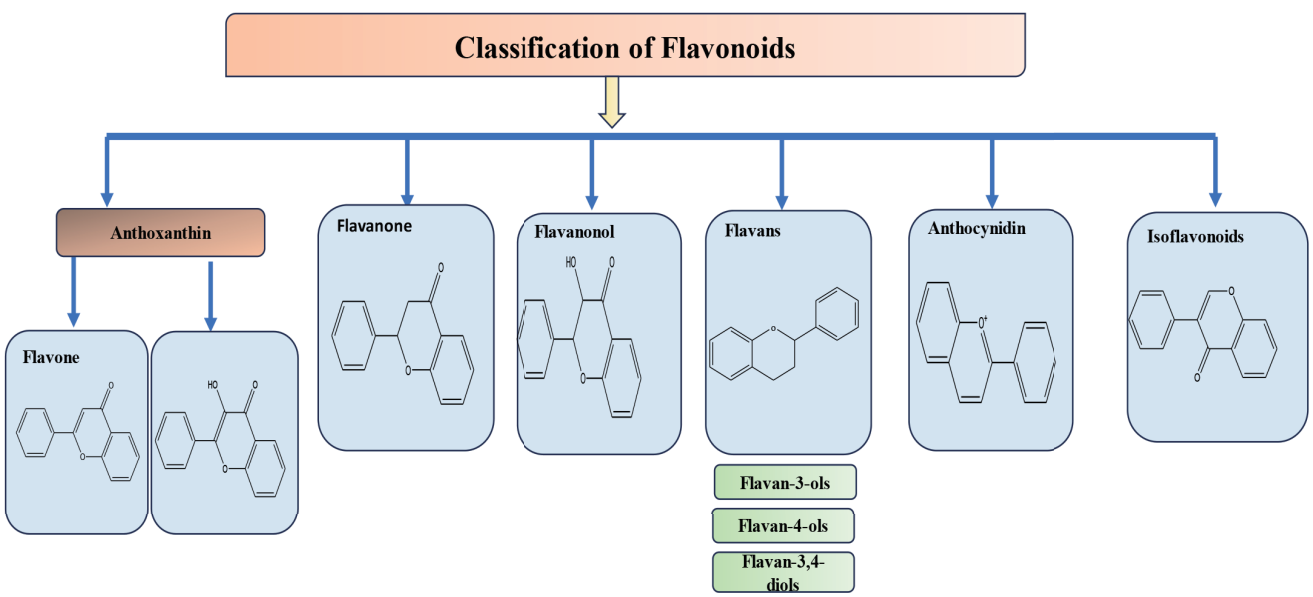
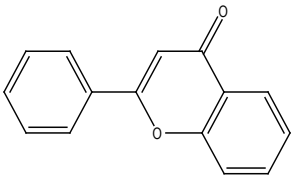
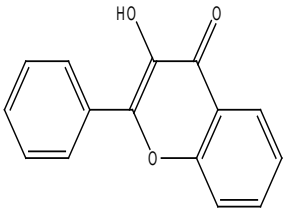
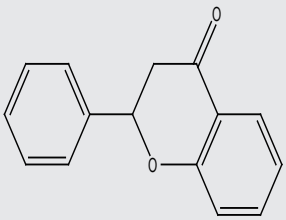
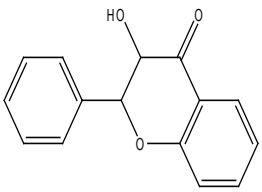
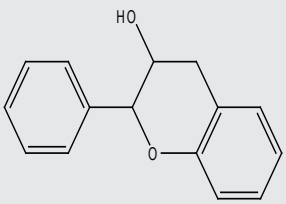
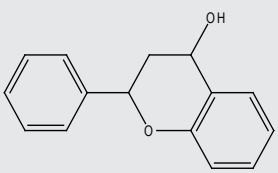
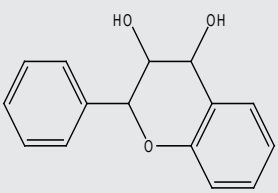
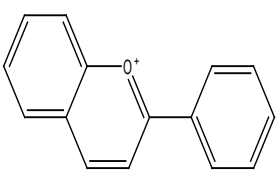
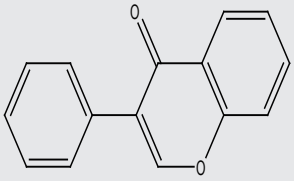


Figure 6: Classification of flavonoids

Table 1: Classification of Flavonoids

Group		Structural Formula	Description	Examples
Anthoxanthin	Flavone		2-phenylchromen-4-one	Baicalein, Apigenin, Chrysin,Luteolin, Wogonin, Acacetin, Vitexin
	Flavonol		3-hydroxy-2-phenylchromen-4-one	Quercetin, Kaempferol, Galangin, Myricetin, Fisetin , Isorhamnetin, Rutin
Flavanones	Flavanone		2,3-dihydro-2-phenylchromen-4-one	Liquiritigenin, Naringin, Hesperetin Blumeatin, Butin, Eriodictyol,
Flavanonols	lavanonol		3-hydroxy-2,3-dihydro-2-phenylchromen-4-one	Taxifolin, Aromadedrin
Flavans	Flavan-3-ol		2-phenyl-3,4-dihydro-2H-chromen-3-ol	Epigallocatechin, Epigallocatechin gallate, Proanthocyanidin, Theaflavin digallate
	Flavan-4-ol		2-phenyl-3,4-dihydro-2H-chromen-4-ol	Apiforol, Luteoforol
	Flavan-3,4-diol		2-phenyl-3,4-dihydro-2H-chromen-3,4-diol	Leucocyanidin, Leucodelphinidin, Leucofisetinidin, Leucomalvidin
Anthocynidins	Anthocynidin		2-phenylchromenyliumion	Delphinidin, Cyanidin, Aurantinidin, Europinidin

Isoflavanoids	Isoflavanes Isoflavenes Isoflavonones Rotenoides Pterocarpans		3-phenylchromen-4-one	Biochanin A, Deguelin Daidzein, Alpinumisoflavone, Genistein,

synergistically with several cell signaling pathways, such as down- and up-regulation of transcription factors, activation/deactivation of membrane receptors, cell signaling regulatory components, and apoptotic cascades[60]. Apigenin also inhibited uptake of glucose in MC3T3-G2/PA6 and U937 cells and inhibit Translocation of GLUT4 and stimulation of AKT[61]. By increasing prolyl hydroxylation of the ODD, chrysin decreases HIF-1α stability and inhibits insulin-induced HIF-1α expression within human prostate cancer cells DU145 . Furthermore, Chrysin inhibits the expression of HIF-1α via interfering with signaling pathway of AKT as well as conjugation among HIF-1α and Hsp90[62]. It has been found that luteolin, inhibits angiogenic signaling mediated by VEGF[8]. This compound decrease transcriptional activity of HIF -1α in HeLa cells. further research show that it impair HIF-1α nuclear accumulation by affecting MAPK pathway[63]. luteolin inhibit activation of Akt and translocation of GLUT4[61]. Flavone, wogonin via PHD, VHL, and Hsp90 regulation inhibits HIF-1α to suppress angiogenesis in MCF-7 cell in vitro and in vivo[64]. Flavon compound such as Acacetin reduces expression of VEGF, HIF-1α, and AKT activation. these two proteins are acacetin's primary downstream targets for preventing VEGF expression in ovarian cancer cells[36]. Vitexin is bioactive flavonoid component, By inhibiting the HMGB1-mediated stimulation of the PI3K/Akt/HIF-1α signaling pathway, vitexin prevented the malignant progression of GC both in vitro and in vivo[37,65] Through PI3K/AKT/mTOR signaling pathway inactivation, vitexin prevents the growth of glioblastoma and non-small cell lung cancer[36,37]Quercetin is special subclass of flavonoid[66] which reduces HIF-1 activity and inhibits tumor development in the HCT116 cancer xenograft model [67]. One common flavonoid kaempferol(9), showed potent inhibitory actions in Huh7 hepatocellular carcinoma cells on HIF-1 activity as a result of p44/p42 MAPK inactivation[68,69] Phosphorylation of HIF-1α is regulated by the PI3K/Akt and p42/p44 MAPK signaling pathways.

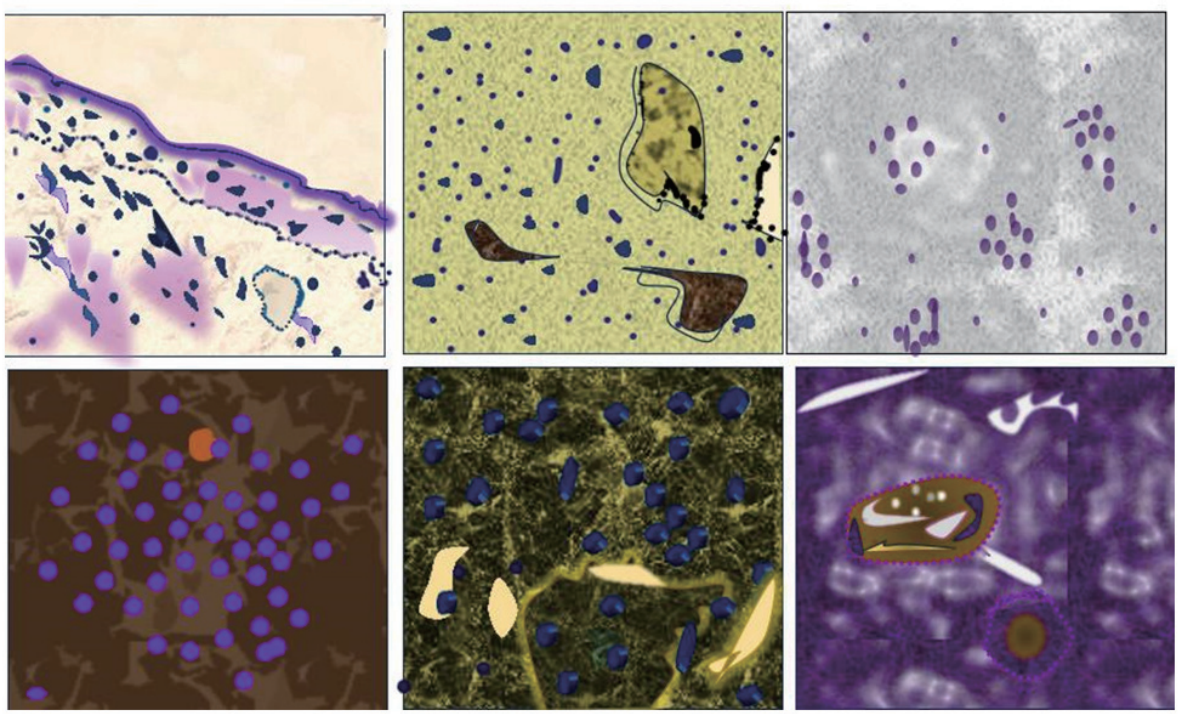


Figure 7: Anthoxanthins as Natural Flavonoids for HIF-1α Inhibitors in Cancer Therapy. Figure shows VEGF expression

kaempferol down-regulates HIF-1α nuclear accumulation and modifies HIF-1 transcriptional activity through interfering with MAPK pathway[70]. Kaempferol also inhibit insulin stimulated glucose uptake in mouse MC3T3-G2/PA6 Cells[61]. OVCAR-3 cell-induced angiogenesis by flavonoids Galangin and Myricetin. The main angiogenesis mediator VEGF was suppressed by galangin and myricetin, and proteins p-Akt, p-p70S6K, and HIF-1α were downregulated in A2780/CP70 and OVCAR-3 cells[71]. Fisetin an dietary flavonoid, has demonstrated strong anti-tumorigenic, anti-invasive, anti-angiogenic effects[72]. Fisetin reduced the low micromolar range of hypoxia-induced VEGF[73]. Fisetin regulated transcriptional

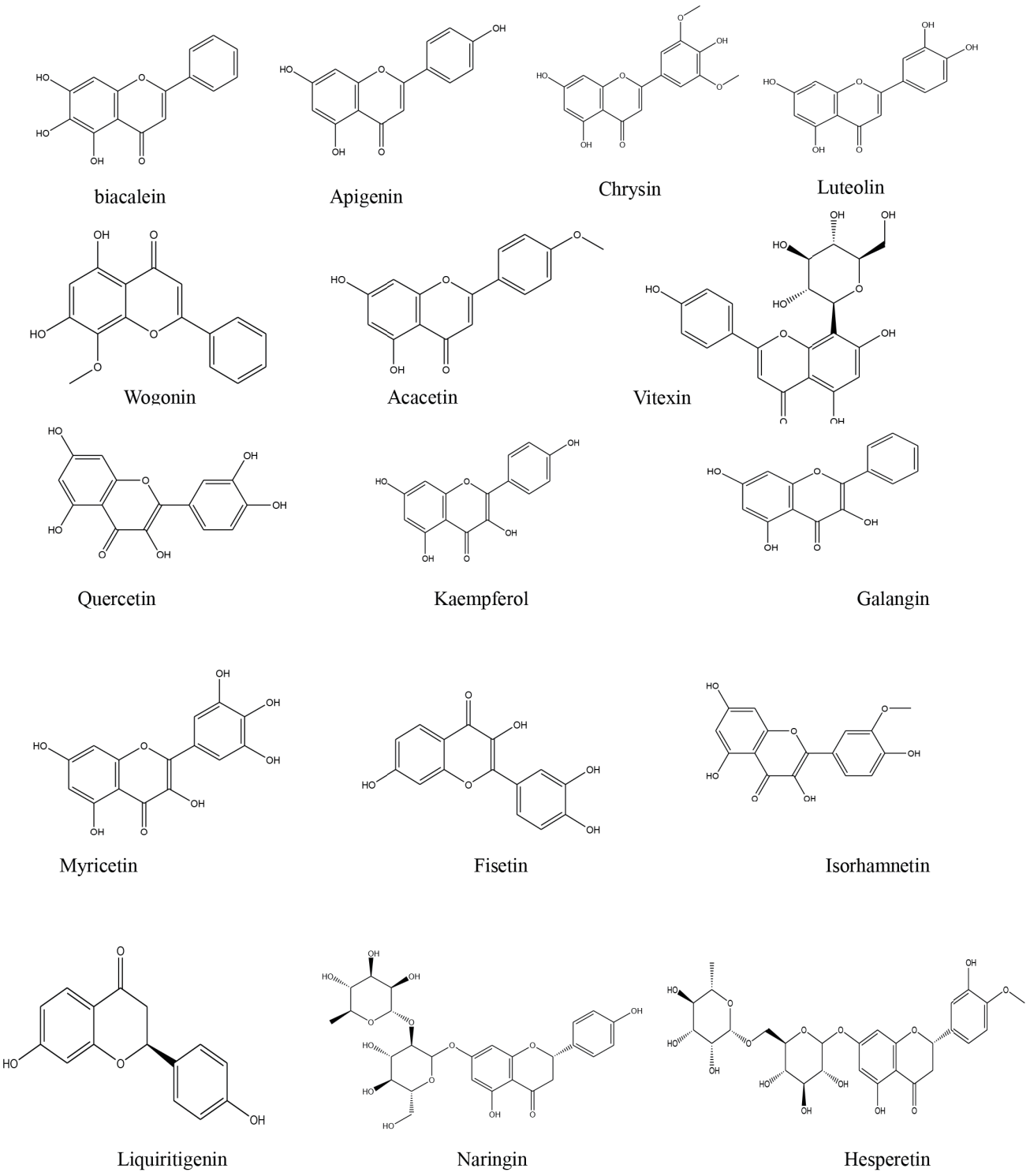


Figure 8: The structure of Flavones, Flavonols, and Flavanones.

activity of HIF-1 and its nuclear accumulation in HeLa cells[74]. Fisetin also inhibit uptake of glucose in U937 and MCT3T3-G2/PA6 cells[61]. Isorhamnetin, one of the most significant active components and it is derivative of quercetin [75,76] In HCT116 and HT29 cells, isorhamnetin greatly inhibited the accumulation of HIF-1α or CoCl2. It suppressed HIF-1α-dependent gene transcription and HRE reporter gene's CoCl2-induced activity. Isorhamnetin also prevented the build-up of HIF-1α caused by H_2O_2[77].

4.2 Flavanone

Liquiritegenin(14), possesses a various anti-cancer properties, suppress HIF-1α and VEGF Expression induced by serum in HeLa cells through the AKT/mTOR-p70S6K signaling pathway[15]. VEGF-mediated tumorigenesis and metastasis may have been inhibited by liquiritigenin's effect on tumor growth[78]. Liquiritigenin has capacity to suppress the kinase activity of MCF-7 and MDA-MB-231 breast cancer cells by interacting directly with VEGFR-2 and enhancing the detoriation of HIF-1α proteasome, which significantly reduces the expression of VEGF[79]. flavonoid naringin is belongs to the Flavanone group [80] (15) extracted from the citrus fruits, has anti-inflammatory, anti-apoptotic, and antioxidant [81,82] Human melanoma cell line A375 and A875 cells naringin suppress the expression of HIF-1α in human melanoma cell line A375 and A875 cells[15]. Hesperetin(16) a phytoestrogen and bioactive substance, it plays vital part in anti-cancer processes[83]. Hespertin inhibits the HIF-1α/VEGF/VEGFR2 signaling pathway in glioma endothelial cells, which prevents angiogenesis in C6 glioma rat cells[84]. it also inhibit glucose uptake in human myelocytic U937 Cell lines[61].

4.3 Flavanonols

The Taxifolin is one of most abundant flavonoide[85], In HepG2 and Huh7 cell lines, treatment with taxifolin, led to the suppression of liver cancer growth. Taxifolin influenced the transcription and translation of HIF-1α, VEGF, and Akt in HepG2 and Huh7 cells, resulting in a substantial reduction in VEGF gene expression[86].

4.4 Flavans

In MCF-7 and MDA-MB-231 cells lactate dehydrogenase A is suppressed by epigallocatechin. This is because it causes Hsp90 to separate from HIF-1α, which accelerates the proteasome's breakdown of HIF-1α[87]. Epigallocatechin-3gallate(EGCG) a bioactive flavonoid [88], in HeLa and HepG2 cells, suppressed hypoxia and serum-induced HIF-1α protein accumulation. VEGF expression was significantly reduced as a result of suppression of HIF-1α protein. By inhibiting the signaling pathways of PI3-kinase/Akt and extracellular signal-regulated kinase½, while also accelerating the degradation of HIF-1α protein via the proteasome system[89]. In lung cancer cell lines, EGCG binding prevents HIF-1α from being ubiquitinated

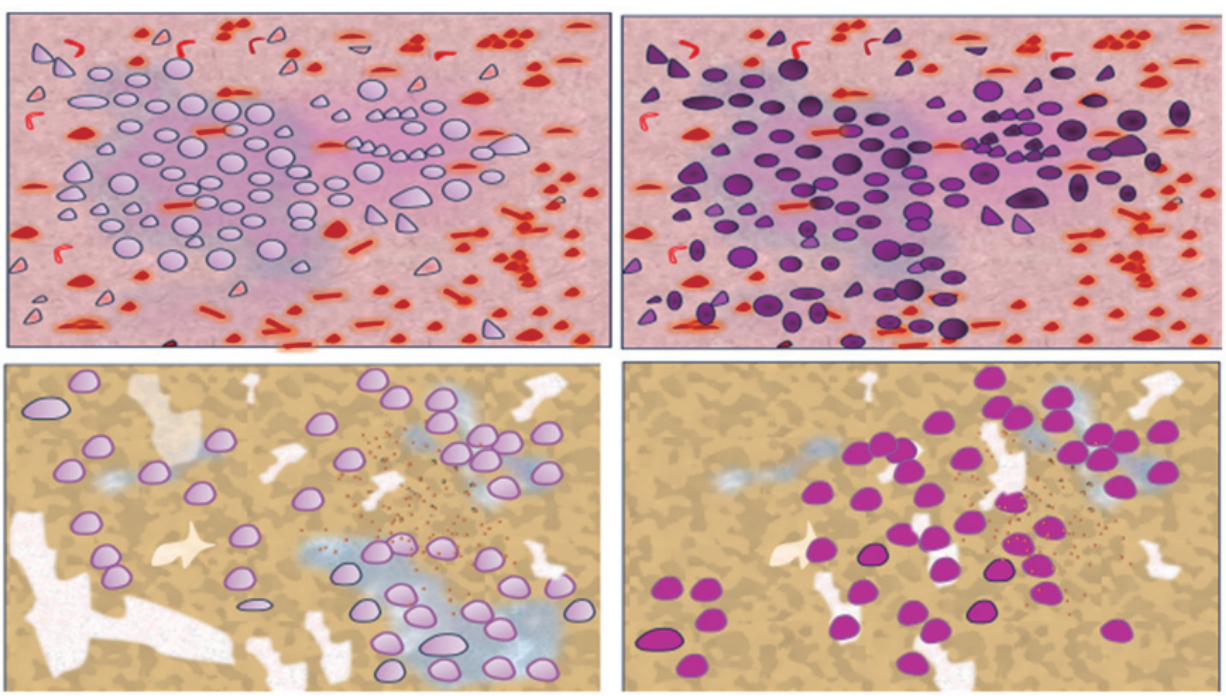


Figure 9: Flavans as Natural Flavonoids for HIF-1α Inhibitors in Cancer Therapy

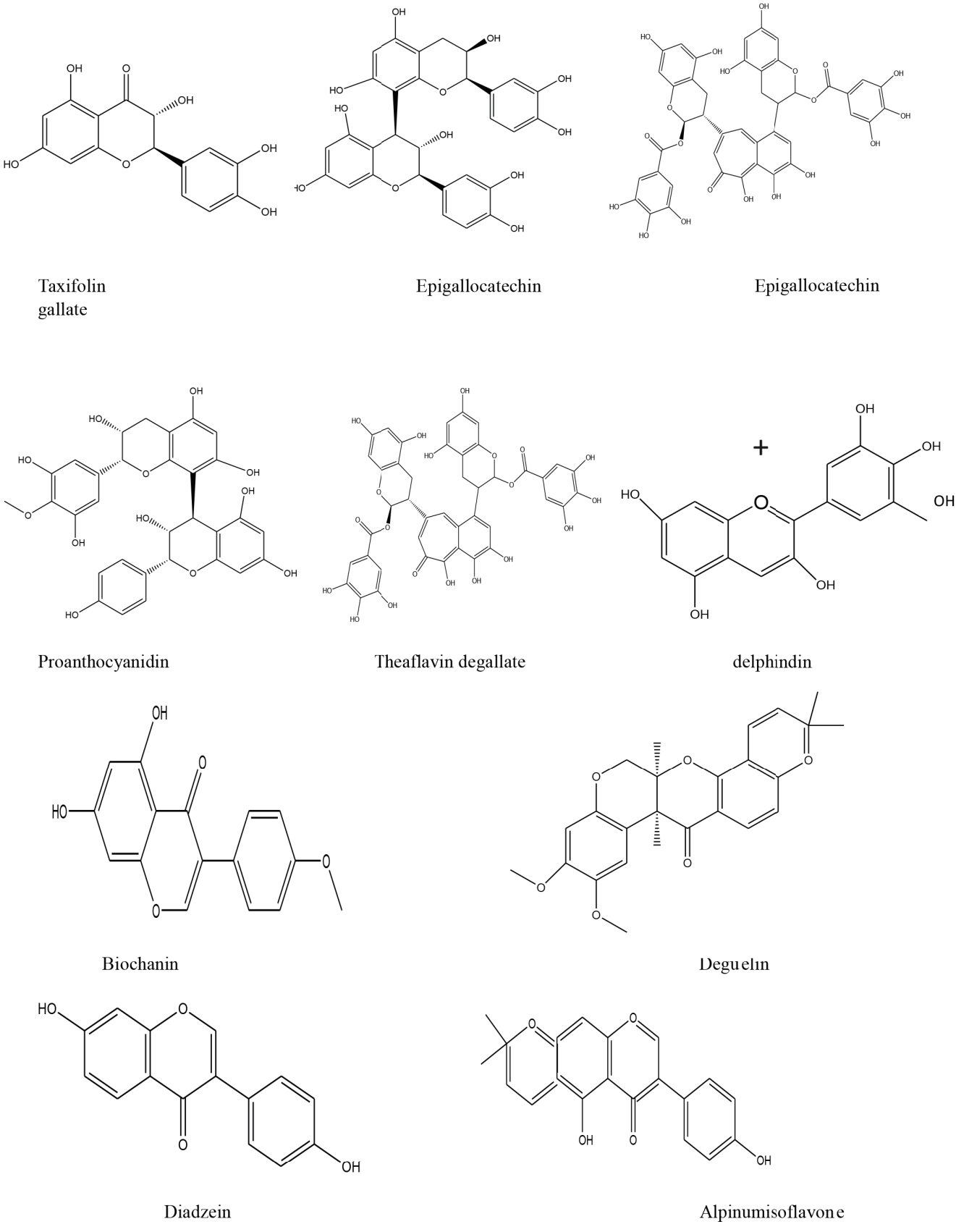


Figure 10: Structure of Flavanonols, Flavanes, Anthocyanidines and Isoflavones.

.This is because it interferes with the hydroxylation of important Pro- residues in the ODD domain[90] . Epigallocatechin gallate also inhibit insulin stimulated uptake of glucose in mouse MC3T3-G2/PA6 Cells[61]. Proanthocyanidine, inhibited angiogenesis in cisplatin-resistant A2780/CP70 cells. It decreased angiogenesis by reducing the VEGF and HIF-1α expression through targeting the Akt/mTOR/p70S6K/4E-BP-1 pathway[91]. It is shown that Theaflavin Digallate rather than EGCG, is more efficient at inhibiting the angiogenesis of tumors produced by human ovarian cancer OVCAR-3 cells by down-regulating HIF-1α and VEGF by inhibiting Akt and Notch-1 pathway's[92].

4.5 Anthocynidines

Delphinidin is compound from the anthocyanidins class[93] , is a polyphenol ,It has significant anticancer effect on the expression of VEGF , in human lung adenocarcinoma A549 cells . Additionally, delphinidin reduced the expression of HIF-1α, a transcription factor of VEGF and HIF-1 binding to the HRE in response to CoCl2 and EGF stimulation. reasearchers discovered that by selectively inhibiting the ERK and PI3K/Akt/mTOR/p70S6K signaling pathway, delphindin reduced the expression of HIF-1 α protein that is activated by Cocl2 and EGF[94].

4.6 Isoflavans

First Biochanin obtained from Trifolium pretense L[95]. It was previously discovered that biochanin A, prevents human glioblastoma cells from invasive. Stimulation of ERK/AKT/mTOR was suppressed, In C6 cells, it also suppressed VEGF and HIF-1α. The chick chorioallantoic membrane assay results demonstrated that ex vivo blood vessel development was suppressed by biochanin A[96]. Deguelin is a rotenoid of the

Table 2: Natural Flavonoids that affect HIF-1α signaling pathway

	Target	Mechanism of HIF-1 inhibition	Cancer cell lines	Reference
Bicalein	Inhibit PI3-Kinase/AKT pathway	Decrease activation of HIF-1α Protein	BV2 Microglia	[58]
Apigenin	Hsp90	HIF-1 production	Ovarian cancer cells	[59]
Chrysin	Hydroxylation of ODD	HIF-1 expression	Prostate cancer cells DU145	[62]
	AKT pathway	HIF-1 expression	Prostate cancer cells DU145	[62]
Lutiolin	MAPK pathway	HIF-1 transcriptional activity	HeLa cells	[63]
Wogonin	PHD, VHL and Hsp90 regulation	HIF-1DNA binding	MCF-7 cells	[64]
Acacetin	AKT/HIF1-α/VEGF PATWAY	HIF-1 Expression	Ovarian cancer cell	[36]
Vitexin	PI3K/Akt/HIF-1α	HIF-1α Inactivation	GC Cells	[37],[65]
	PI3K/AKT/mTOR	HIF-1α Inactivation	Glioblastoma and non small cell	[36],[37]
Quercetin		HIF-1α activity	HCT116 Cells	[67]
Kaemprofel	P44/p42 MAPK Pathway	Decrease HIF1-α activity	Huh7 Hepatocellular carcinoma cell	[70]
Galangin and Myricetin	VEGF	Downregulation of HIF1-α	A27/80 And CP70 and OVACAR-3 cells	[71]
Fisetin		Inhibit HIF1-α Accumulation	HELA cells	[74]
Isorhamnetine		Inhibit HIF1-α Accumulation	HCT116 and HT29 cells	[77]
Liquiritigenin	AKT/mTOR-p70S6K Pathway	HIF-1α supression	HeLa cells	[15]

	HIF-1α Proteasome and VEGFR2	HIF-1α Expression	MDA-MB-231 cells	[79]
Naringin		HIF-1α Expression	A375 cells ; A875 cells	[15]
Hesperetin	HIF-1α/VEGF/VEGFR2 signaling pathway	stability of HIF-1α	Glioma endothelial cells	[84]
Taxifoline	VEGF, AKT, HIF-1α	HIF-1α Expression influenced	HepG2 and Huh7	[86]
Epigallocatechin	Hsp90-HIF-1α	Expression of HIF-1α	MCF-7 and MDA-MB-231 cells	[87]
Epigallocatechin Gallate	PI-3/Akt and HIF-1α Proteosome	HIF-1α accumulation	HeLa and HepG2 cells	[89]
Proanthocyanidine	Akt/mTOR/p70S6K/4E-BP-1 pathway	HIF-1α expression	A2780/CP70 cells	[91]
Theaflavin digallate	Akt and Notch-1 pathway's	HIF-1α Downregulation	Human ovarian cancer OVCAR-3 cell	[92]
Delphindin	VEGF	HIF-1α Expression	Human lung adenocarcinoma A549 cells	[94]
Biochanin	ERK/AKT/mTOR	Suppression of HIF-1α	C6 cells	[96]
Degueline	VEGF	HIF-1α expression	HNSCC and SCLC	[98]
Diadzein	APE1/Ref-1,NF-κB, and HIF-1α	HIF-1α expression	AR+ and AR-PCa cells	[99]
Alpinumisoflavon		Suppression of HIF-1α	Human breast carcinoma T47D cells	[101]

flavonoid family [97], therapeutic effectiveness in treating aerodigestive tract cancers, such as head and neck squamous cell carcinoma (HNSCC) and nonsmall cell lung cancer (NSCLC), deguelin effectively reduces VEGF production and inhibits HIF-1α expression at the translational and post-translational levels in vitro and in vivo. These actions lead to antiangiogenic and therapeutic effects[98]. By preventing ATP binding, it disrupts the chaperone role of HSP90. This leads to the instability of HIF-1α and a reduction in tumor growth in xenograft models of different human malignancies[95,96]. Daidzein soy component that inhibits metastasis caused by genistein. In AR+ and AR-PCa cells, daidzein decreased cell development and reacted synergistically with radiation to impact APE1/Ref-1, NFκB, and HIF-1α[99]. Daidzein suppresses genes necessary for angiogenesis and tumor growth, as demonstrated as the inhibition of VEGF production and creation of tubes in HUVECs[100]. Daidzein also inhibit uptake of glucose in U937 Cell lines[61]. Alpinumisoflavone in human breast carcinoma T47D cells , It suppresses hypoxia-induced HIF-1 activation[101].

5. Discussion

The evidence underscores the potential of natural flavonoids as HIF-1α inhibitors in cancer therapy. Their multi-faceted mechanisms of action, combined with low toxicity, position them as promising agents in the treatment of tumor hypoxia. However, further research is needed to optimize flavonoid derivatives for clinical use and to explore their integration into multi-target therapeutic strategies. The findings support the inclusion of HIF-1α as a critical target in the development of inhibitors addressing tumor vascularization and glycolysis, offering new directions for cancer treatment.

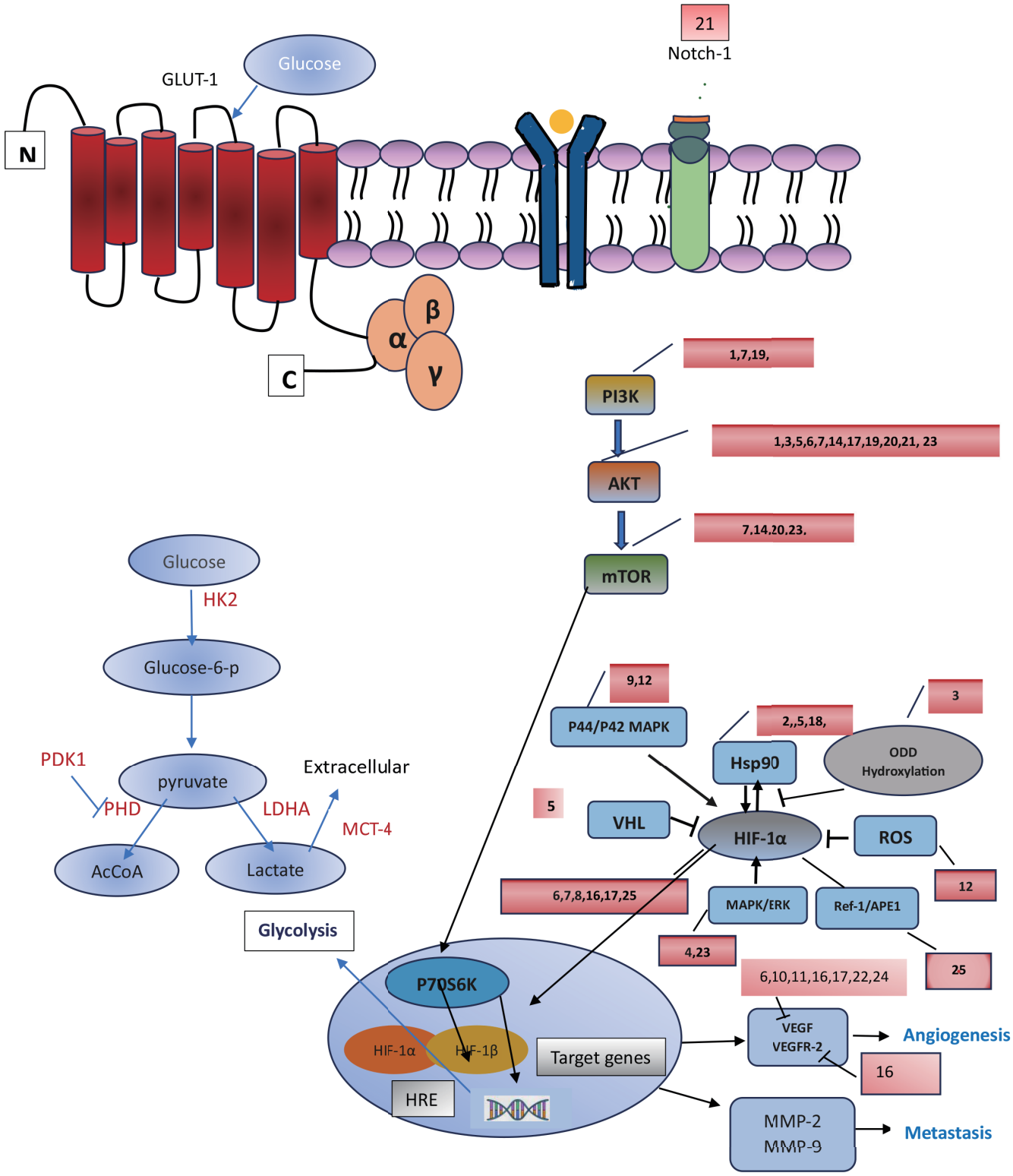


Figure 11: HIF-1 signaling pathway. The HIF-1α signaling pathway involved in the inhibition of angiogenesis, glycolysis and metastasis bynaturalflavonoids. AcCoA: acetyl coenzyme A; AKT: protein kinase B (PKB); Glucose-6-P: Glucose-6-Phosphate; GLUT-1: glucose transporter 1; HRE: hypoxia response elements; HSP90: heat shock protein 90; MAPK: mitogen activated protein kinase; mTOR: mammalian target of rapamycin; VEGF: vascular endothelial growth factor; p70S6K: ribosomal protein S6 kinase beta-1; PI3K:phosphatidylinositol-3-kinase.

6. Conclusion

The clinical effectiveness of wide range of currently available anticancer drugs is being reduced by rising recurrence of mammalian malignancies and the severe adverse effects of chemotherapy, less stability and lower bioavaibility. Therefore, to increase the survival rate of cancer patients, it is essential to find new and effective anticancer medications. HIF-1 alpha is essential for the reprogramming of cancer cells' metabolism. Its effects include suppressing the VEGF-induced angiogenesis and survival-promoting signaling pathway, as well as controlling the expression of genes encoding glucose transporters. Alternative cancer treatments include inhibiting the HIF-1α signaling pathway with solid tumors by interfere with HIF-1α induced angiogenesis under hypoxic environment. Flavonoides appear to be a potent chemopreventive agent and exhibit a broad variety of biological actions. According to earlier study, the data in the review demonstrated the molecular mechanisms of various flavonoids and suggested whether the flavonoid may be structurally modified to totally inhibit glycolysis and tumor blood vessels at the same time. Moreover, Furthermore, the majority of naturally occurring flavonoides are poorly stable, poorly bioavailable, and poorly soluble in fat. in order to improve the mentioned properties, the natural flavonoids could be structurally changed. In this review in order to increase bioavailability and solubility and to better understand the impact of anticancer flavonoids on HIF-1 alpha, amino acids or amino groups were added to the flavonoid structure. understanding the effect of anticancer flavonoids on HIF-1 α may be relevant in the development of novel compounds with increased anticancer activity.

Abbreviations

HIF-1α: Hypoxia inducible factor one alpha;
HIF-1β: Hypoxia inducible factor one beta;
bHLH: Helix loop helix domain;
PAS: per-ARNT-sim Domains;
ODD: Oxygen dependent degradation domain;
PHD-2: Prolyl hydroxylase 2;
VHL: Von Hipel Lindau;
HRE: Hypoxia response element;
MAPK: Mitogen activated protein kinase;
PI3K: Phosphatidylinositol 3 kinase;
VEGF: Vascular endothelial growth factor;
BE: Baicalein;
AKT: Protein kinase B;
GLUT: Glucose transporter;
HSP: Heat shock protein;
ROS: Reactive oxygen species;
LDH A: Lactate dehydrogenase A;
EGCG: Epigallocatechin gallate;
HNSCC: Head and neck squamous cell carcinoma;
NSCLC: Nonsmall cell lung cancer.

Consent for Publication

Not applicable.

Availability

The dataset used and analysed during current study available from the corresponding author on reasonable request.

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Conflict Interest

The authors declare that they have no conflict of interests.

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Author Contribution

The author contributed to the idea and design of the review, with drafting of article and revision of article.

References

1 A. Singh, "Cancer: Unraveling the Complexities of Uncontrolled Growth and Metastasis," no. 8, pp. 158–175, 2023, doi: 10.5281/zenodo.8266559.
2 D. Singh, M. Gupta, M. Sarwat, and H. R. Siddique, "Apigenin in cancer prevention and therapy: A systematic review and meta-analysis of animal models," Crit. Rev. Oncol. Hematol., vol. 176, p. 103751, 2022, doi: https://doi.org/10.1016/j.critrevonc.2022.103751.
3 H. M. Bizuayehu et al., "Global Disparities of Cancer and Its Projected Burden in 2050.," JAMA Netw. open, vol. 7, no. 11, p. e2443198, 2024, doi: 10.1001/jamanetworkopen.2024.43198.
4 A. Sofuni and T. Itoi, "Current status and future perspective of sonodynamic therapy for cancer," J. Med. Ultrason., 2022, doi: 10.1007/s10396-022-01263-x.
5 Z. Zhou and M. Li, "Targeted therapies for cancer," BMC Med., vol. 20, no. 1, pp. 1–3, 2022, doi: 10.1186/s12916-022-02287-3.
6 S. Gavas, S. Quazi, and T. M. Karpiński, "Nanoparticles for Cancer Therapy: Current Progress and Challenges," Nanoscale Res. Lett., vol. 16, no. 1, 2021, doi: 10.1186/

s11671-021-03628-6.
7 J. Han, B. Zhang, S. Zheng, Y. Jiang, X. Zhang, and K. Mao, "The Progress and Prospects of Immune Cell Therapy for the Treatment of Cancer," Cell Transplant., vol. 33, 2024, doi: 10.1177/09636897241231892.
8 E. Ansó, A. Zuazo, M. Irigoyen, M. C. Urdaci, A. Rouzaut, and J. J. Martínez-Irujo, "Flavonoids inhibit hypoxia-induced vascular endothelial growth factor expression by a HIF-1 independent mechanism," Biochem. Pharmacol., vol. 79, no. 11, pp. 1600–1609, 2010, doi: 10.1016/j.bcp.2010.02.004.
9 N. Shen, T. Wang, Q. Gan, S. Liu, L. Wang, and B. Jin, "Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity," Food Chem., vol. 383, p. 132531, 2022, doi: https://doi.org/10.1016/j.foodchem.2022.132531.
10 M. Cárdenas, M. Marder, V. C. Blank, and L. P. Roguin, "Antitumor activity of some natural flavonoids and synthetic derivatives on various human and murine cancer cell lines," Bioorg. Med. Chem., vol. 14, no. 9, pp. 2966–2971, 2006, doi: https://doi.org/10.1016/j.bmc.2005.12.021.
11 G. Galati and P. J. O'Brien, "Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties," Free Radic. Biol. Med., vol. 37, no. 3, pp. 287–303, 2004, doi: https://doi.org/10.1016/j.freeradbiomed.2004.04.034.
12 B. P. George, R. Chandran, and H. Abrahamse, "Role of phytochemicals in cancer chemoprevention: Insights," Antioxidants, vol. 10, no. 9, 2021, doi: 10.3390/antiox10091455.
13 G. K. Subbaraj, Y. S. Kumar, and L. Kulanthaivel, "Antiangiogenic role of natural flavonoids and their molecular mechanism: an update," Egypt. J. Intern. Med., vol. 33, no. 1, p. 29, 2021, doi: 10.1186/s43162-021-00056-x.
14 P. A. Newcomb and P. P. Carbone, "Cancer Treatment and Age: Patient Perspectives," JNCI J. Natl. Cancer Inst., vol. 85, no. 19, pp. 1580–1584, Oct. 1993, doi: 10.1093/jnci/85.19.1580.
15 X. Deng et al., "Anticancer Activity of Natural Flavonoids: Inhibition of HIF-1α Signaling Pathway," Curr. Org. Chem., vol. 23, no. 26, pp. 2945–2959, 2019, doi: 10.2174/1385272823666191203122030.
16 R. Abou Khouzam et al., "Tumor Hypoxia Regulates Immune Escape/Invasion: Influence on Angiogenesis and Potential Impact of Hypoxic Biomarkers on Cancer Therapies," Front. Immunol., vol. 11, no. January, pp. 1–16, 2021, doi: 10.3389/fimmu.2020.613114.
17 Y. Xia, H.-K. Choi, and K. Lee, "Recent advances in hypoxia-inducible factor (HIF)-1 inhibitors," Eur. J. Med. Chem., vol. 49, pp. 24–40, 2012, doi: https://doi.org/10.1016/j.ejmech.2012.01.033.
18 V. Infantino, A. Santarsiero, P. Convertini, S. Todisco, and V. Iacobazzi, "Cancer cell metabolism in hypoxia: Role of HIF-1 as key regulator and therapeutic target," Int. J. Mol. Sci., vol. 22, no. 11, 2021, doi: 10.3390/ijms22115703.
19 I. E. Pralea et al., "Phytochemicals as Regulators of Tumor Glycolysis and Hypoxia Signaling Pathways: Evidence from In Vitro Studies," Pharmaceuticals, vol. 15, no. 7, pp. 1–36, 2022, doi: 10.3390/ph15070808.
20 L. Zhan et al., "Phytochemicals targeting glycolysis in colorectal cancer therapy: effects and mechanisms of action," Front. Pharmacol., vol. 14, no. August, 2023, doi: 10.3389/fphar.2023.1257450.
21 M. Rashid et al., "Up-down regulation of HIF-1α in cancer progression," Gene, vol. 798, p. 145796, 2021, doi: https://doi.org/10.1016/j.gene.2021.145796.
22 P. S. Mishra, R. Mishra, V. M. Patil, and S. Dewangan, "Role of natural secondary metabolites as HIF-1 inhibitors in cancer therapy," Med. Chem. Res., vol. 33, no. 5, pp. 721–734, 2024, doi: 10.1007/s00044-024-03219-x.
23 S. Mirzaei, B. Ranjbar, S. H. Tackallou, and A. R. Aref, "Hypoxia inducible factor-1α (HIF-1α) in breast cancer: The crosstalk with oncogenic and onco-suppressor factors in regulation of cancer hallmarks," Pathol. - Res. Pract., vol. 248, p. 154676, 2023, doi: https://doi.org/10.1016/j.prp.2023.154676.
24 Y. Yang et al., "Molecular characterization and expression analysis of hypoxia-inducible factor-1α, factor-2α, and factor-3α and physiological response to hypoxia exposure in Amur minnow (Phoxinus lagowskii)," Aquac. Int., vol. 30, no. 2, pp. 607–632, 2022, doi: 10.1007/s10499-021-00826-y.
25 C. YANG, Z. F. ZHONG, S. P. WANG, C. T. VONG, B. YU, and Y. T. WANG, "HIF-1: structure, biology and natural modulators," Chinese J. Nat. Med. , vol. 19, no. 7, pp. 521–527, 2021, doi: 10.1016/S1875-5364(21)60051-1.
26 S. M. T. Islam, J. Won, M. Khan, M. D. Mannie, and I. Singh, "Hypoxia-inducible factor-1 drives divergent immunomodulatory functions in the pathogenesis of autoimmune diseases," Immunology, vol. 164, no. 1, pp. 31–42, 2021, doi: 10.1111/imm.13335.
27 Q. Chu, X. Gu, Q. Zheng, and H. Zhu, "Regulatory mechanism of HIF-1α and its role in liver diseases: a narrative review.," Ann. Transl. Med., vol. 10, no. 2, p. 109, Jan. 2022, doi: 10.21037/atm-21-4222.
28 X. Huang, L. Zhao, and R. Peng, "Hypoxia-Inducible Factor 1 and Mitochondria: An Intimate Connection," Biomolecules, vol. 13, no. 1, pp. 1–14, 2023, doi: 10.3390/biom13010050.
29 P. Cytokines, M. I. Malkov, C. T. Lee, and C. T. Taylor, "Regulation of the Hypoxia-Inducible Factor (HIF) by," pp. 1–15, 2021.
30 F. Locatelli, R. Minutolo, L. De Nicola, and L. Del Vecchio, "Evolving Strategies in the Treatment of Anaemia in Chronic Kidney Disease: The HIF-Prolyl Hydroxylase Inhibitors," Drugs, vol. 82, no. 16, pp. 1565–1589, 2022, doi: 10.1007/s40265-022-01783-3.
31 M. Jaśkiewicz et al., "The transition from HIF-1 to HIF-2 during prolonged hypoxia results from reactivation of PHDs and HIF1A mRNA instability," Cell. Mol. Biol. Lett., vol. 27, no. 1, 2022, doi: 10.1186/s11658-022-00408-7.
32 S. Rani, S. Roy, M. Singh, and G. Kaithwas, "Regulation of Transactivation at C-TAD Domain of HIF-1 α by Factor-Inhibiting HIF-1 α (FIH-1): A Potential Target for

Therapeutic Intervention in Cancer," Oxid. Med. Cell. Longev., vol. 2022, 2022, doi: 10.1155/2022/2407223.
33 J. E. Ziello, I. S. Jovin, and Y. Huang, "Hypoxia-Inducible Factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia," Yale J. Biol. Med., vol. 80, no. 2, pp. 51–60, 2007.
34 S. Mazumder, P. J. Higgins, and R. Samarakoon, "Downstream Targets of VHL/HIF-α Signaling in Renal Clear Cell Carcinoma Progression: Mechanisms and Therapeutic Relevance," Cancers (Basel)., vol. 15, no. 4, pp. 1–23, 2023, doi: 10.3390/cancers15041316.
35 V. Kumar, G. K. K. Viswanathan, K. Ralhan, E. Gazit, and D. Segal, "Amyloidogenic Properties of Peptides Derived from the VHL Tumor Suppressor Protein," ChemMedChem, vol. 16, no. 23, pp. 3565–3568, 2021, doi: 10.1002/cmdc.202100441.
36 L. Z. Liu et al., "Acacetin inhibits VEGF expression, tumor angiogenesis and growth through AKT/HIF-1α pathway," Biochem. Biophys. Res. Commun., vol. 413, no. 2, pp. 299–305, 2011, doi: 10.1016/j.bbrc.2011.08.091.
37 K. Ganesan and B. Xu, "Molecular targets of vitexin and isovitexin in cancer therapy: a critical review," Ann. N. Y. Acad. Sci., vol. 1401, no. 1, pp. 102–113, 2017, doi: 10.1111/nyas.13446.
38 A. Cabaj, A. Moszyńska, A. Charzyńska, R. Bartoszewski, and M. Dąbrowski, "Functional and HRE motifs count analysis of induction of selected hypoxia-responsive genes by HIF-1 and HIF-2 in human umbilical endothelial cells," Cell. Signal., vol. 90, p. 110209, 2022, doi: https://doi.org/10.1016/j.cellsig.2021.110209.
39 Y. Wang, H. Wu, and R. Deng, "Angiogenesis as a potential treatment strategy for rheumatoid arthritis," Eur. J. Pharmacol., vol. 910, p. 174500, 2021, doi: https://doi.org/10.1016/j.ejphar.2021.174500.
40 J. Maphutha, D. Twilley, and N. Lall, "The Role of the PTEN Tumor Suppressor Gene and Its Anti-Angiogenic Activity in Melanoma and Other Cancers," Molecules, vol. 29, no. 3, pp. 1–19, 2024, doi: 10.3390/molecules29030721.
41 M. M. Hickey and M. C. B. T.-C. T. in D. B. Simon, "Regulation of Angiogenesis by Hypoxia and Hypoxia-Inducible Factors," vol. 76, Academic Press, 2006, pp. 217–257. doi: https://doi.org/10.1016/S0070-2153(06)76007-0.
42 G. Powis and L. Kirkpatrick, "Hypoxia inducible factor-1α as a cancer drug target," Mol. Cancer Ther., vol. 3, no. 5, pp. 647–654, 2004, doi: 10.1158/1535-7163.647.3.5.
43 S. Xiao et al., "Adolescent exposure to organophosphate insecticide malathion induces spermatogenesis dysfunction in mice by activating the HIF-1/MAPK/PI3K pathway," Environ. Pollut., vol. 363, p. 125209, 2024, doi: https://doi.org/10.1016/j.envpol.2024.125209.
44 D. Wang et al., "Effects of HIF-1α on Spermatogenesis of Varicocele Rats by Regulating VEGF/PI3K/Akt Signaling Pathway," Reprod. Sci., vol. 28, no. 4, pp. 1161–1174, 2021, doi: 10.1007/s43032-020-00395-0.
45 P. Fojtík, D. Beckerová, K. Holomková, M. Šenfluk, and V. Rotrekl, "Both Hypoxia-Inducible Factor 1 and MAPK Signaling Pathway Attenuate PI3K/AKT via Suppression of Reactive Oxygen Species in Human Pluripotent Stem Cells," Front. Cell Dev. Biol., vol. 8, no. January, pp. 1–18, 2021, doi: 10.3389/fcell.2020.607444.
46 W. Cheng, Z. Cheng, L. Weng, D. Xing, and M. Zhang, "Asparagus Polysaccharide inhibits the Hypoxia-induced migration, invasion and angiogenesis of Hepatocellular Carcinoma Cells partly through regulating HIF1α/VEGF expression via MAPK and PI3K signaling pathway.," J. Cancer, vol. 12, no. 13, pp. 3920–3929, 2021, doi: 10.7150/jca.51407.
47 M. Kuntjoro et al., "Cobalt Chloride as a Hypoxia Mimicking Agent Induced HIF-1α and mTOR Expressions of Human Umbilical Cord Mesenchymal Stem Cells," Pesqui. Bras. Odontopediatria Clin. Integr., vol. 24, pp. 1–10, 2024, doi: 10.1590/pboci.2024.020.
48 C. Treins, S. Giorgetti-Peraldi, J. Murdaca, M. N. Monthouël-Kartmann, and E. Van Obberghen, "Regulation of hypoxia-inducible factor (HIF)-1 activity and expression of HIF hydroxylases in response to insulin-like growth factor I," Mol. Endocrinol., vol. 19, no. 5, pp. 1304–1317, 2005, doi: 10.1210/me.2004-0239.
49 M. Mesuraca, B. Quaresima, S. Scicchitano, and M. C. Faniello, "Special Issue 'Molecular Advances in Cancer and Cell Metabolism,'" Int. J. Mol. Sci., vol. 26, no. 5, pp. 1–4, 2025, doi: 10.3390/ijms26051876.
50 Prithviraj Karak, "Biological Activities of Flavonoids: an Overview," Int. J. Pharm. Sci. Res. , vol. 10, no. 4, pp. 1567–1574, 2019, doi: 10.13040/IJPSR.0975-8232.10(4).1567-74.
51 K. Zhai, A. Mazurakova, L. Koklesova, P. Kubatka, and D. Büsselberg, "Flavonoids synergistically enhance the anti-glioblastoma effects of chemotherapeutic drugs," Biomolecules, vol. 11, no. 12, 2021, doi: 10.3390/biom11121841.
52 H. Tao et al., "Comparative metabolomics of flavonoids in twenty vegetables reveal their nutritional diversity and potential health benefits," Food Res. Int., vol. 164, p. 112384, 2023, doi: https://doi.org/10.1016/j.foodres.2022.112384.
53 Y. Fu, W. Liu, and O. P. Soladoye, "Towards innovative food processing of flavonoid compounds: Insights into stability and bioactivity," Lwt, vol. 150, no. June, 2021, doi: 10.1016/j.lwt.2021.111968.
54 D. M. Kopustinskiene, V. Jakstas, A. Savickas, and J. Bernatoniene, "Flavonoids as Anticancer Agents," no. C, pp. 1–25, 2020.
55 M.-M. Li, Y.-T. Chen, J.-C. Ruan, W.-J. Wang, J.-G. Chen, and Q.-F. Zhang, "Structure-activity relationship of dietary flavonoids on pancreatic lipase," Curr. Res. Food Sci., vol. 6, p. 100424, 2023, doi: https://doi.org/10.1016/j.crfs.2022.100424.
56 S. . . c.k. kokate, A.P. purohit, pharmacognocy.
57 C. Lei et al., "The most recent progress of baicalein in its anti-neoplastic effects and mechanisms," Biomed. Pharmacother., vol. 176, p. 116862, 2024, doi: https://doi.org/10.1016/j.biopha.2024.116862.

58 K. Y. Hwang et al., "Baicalein suppresses hypoxia-induced HIF-1α protein accumulation and activation through inhibition of reactive oxygen species and PI 3-kinase/Akt pathway in BV2 murine microglial cells," Neurosci. Lett., vol. 444, no. 3, pp. 264–269, 2008, doi: https://doi.org/10.1016/j.neulet.2008.08.057.
59 J. Fang et al., "Apigenin inhibits tumor angiogenesis through decreasing HIF-1α and VEGF expression," Carcinogenesis, vol. 28, no. 4, pp. 858–864, 2007, doi: 10.1093/carcin/bgl205.
60 Z. Nozhat, S. Heydarzadeh, Z. Memariani, and A. Ahmadi, "Chemoprotective and chemosensitizing effects of apigenin on cancer therapy," Cancer Cell Int., vol. 21, no. 1, pp. 1–26, 2021, doi: 10.1186/s12935-021-02282-3.
61 J. Gao and Y. Chen, "Natural Compounds Regulate Glycolysis in Hypoxic Tumor Microenvironment," vol. 2015, 2015.
62 B. Fu, J. Xue, Z. Li, X. Shi, B. H. Jiang, and J. Fang, "Chrysin inhibits expression of hypoxia-inducible factor 1-α through reducing hypoxia-inducible factor-1α stability and inhibiting its protein synthesis," Mol. Cancer Ther., vol. 6, no. 1, pp. 220–226, 2007, doi: 10.1158/1535-7163.MCT-06-0526.
63 A. Triantafyllou, I. Mylonis, G. Simos, S. Bonanou, and A. Tsakalof, "Flavonoids induce HIF-1α but impair its nuclear accumulation and activity," Free Radic. Biol. Med., vol. 44, no. 4, pp. 657–670, 2008, doi: 10.1016/j.freeradbiomed.2007.10.050.
64 X. Song et al., "Wogonin inhibits tumor angiogenesis via degradation of HIF-1α protein," Toxicol. Appl. Pharmacol., vol. 271, no. 2, pp. 144–155, 2013, doi: https://doi.org/10.1016/j.taap.2013.04.031.
65 P. Zhou, Z. Zheng, T. Wan, J. Wu, C. Liao, and X. Sun, "Vitexin Inhibits Gastric Cancer Growth and Metastasis through HMGB1- mediated Inactivation of the PI3K / AKT / mTOR / HIF-1 α Signaling Pathway," vol. 21, no. 4, pp. 439–456, 2021.
66 P. Singh, Y. Arif, A. Bajguz, and S. Hayat, "The role of quercetin in plants," Plant Physiol. Biochem., vol. 166, pp. 10–19, 2021, doi: https://doi.org/10.1016/j.plaphy.2021.05.023.
67 H. S. Kim et al., "Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of AMPK activity in HCT116 colon cancer," Apoptosis, vol. 17, no. 9, pp. 938–949, 2012, doi: 10.1007/s10495-012-0719-0.
68 J. Ren, Y. Lu, Y. Qian, B. Chen, T. Wu, and G. Ji, "Recent progress regarding kaempferol for the treatment of various diseases (Review)," Exp. Ther. Med., pp. 2759–2776, 2019, doi: 10.3892/etm.2019.7886.
69 I. Mylonis, A. Lakka, A. Tsakalof, and G. Simos, "The dietary flavonoid kaempferol effectively inhibits HIF-1 activity and hepatoma cancer cell viability under hypoxic conditions," Biochem. Biophys. Res. Commun., vol. 398, no. 1, pp. 74–78, 2010, doi: https://doi.org/10.1016/j.bbrc.2010.06.038.
70 B. Manolescu, E. Oprea, C. Busu, and C. Cercasov, "Natural compounds and the hypoxia-inducible factor (HIF) signalling pathway," Biochimie, vol. 91, no. 11–12, pp. 1347–1358, 2009, doi: 10.1016/j.biochi.2009.08.005.
71 H. Zalpoor, M. Bakhtiyari, M. Liaghat, M. Nabi-Afjadi, and M. Ganjalikhani-Hakemi, "Quercetin potential effects against SARS-CoV-2 infection and COVID-19-associated cancer progression by inhibiting mTOR and hypoxia-inducible factor-1α (HIF-1α).," Phytotherapy research : PTR, vol. 36, no. 7. England, pp. 2679–2682, Jul. 2022. doi: 10.1002/ptr.7440.
72 H. C. Pal, R. L. Pearlman, and F. Afaq, "Fisetin and Its Role in Chronic Diseases BT - Anti-inflammatory Nutraceuticals and Chronic Diseases," S. C. Gupta, S. Prasad, and B. B. Aggarwal, Eds., Cham: Springer International Publishing, 2016, pp. 213–244. doi: 10.1007/978-3-319-41334-1_10.
73 E. Ansó, A. Zuazo, M. Irigoyen, M. C. Urdaci, A. Rouzaut, and J. J. Martínez-Irujo, "Flavonoids inhibit hypoxia-induced vascular endothelial growth factor expression by a HIF-1 independent mechanism," Biochem. Pharmacol., vol. 79, no. 11, pp. 1600–1609, 2010, doi: https://doi.org/10.1016/j.bcp.2010.02.004.
74 N. Afroze et al., "Fisetin Deters Cell Proliferation, Induces Apoptosis, Alleviates Oxidative Stress and Inflammation in Human Cancer Cells, HeLa," Int. J. Mol. Sci., vol. 23, no. 3, 2022, doi: 10.3390/ijms23031707.
75 G. Gong et al., "Isorhamnetin: A review of pharmacological effects," Biomed. Pharmacother., vol. 128, p. 110301, 2020, doi: https://doi.org/10.1016/j.biopha.2020.110301.
76 P. Biswas et al., "The experimental significance of isorhamnetin as an effective therapeutic option for cancer: A comprehensive analysis," Biomed. Pharmacother., vol. 176, p. 116860, 2024, doi: https://doi.org/10.1016/j.biopha.2024.116860.
77 S. Seo, K. Seo, S. H. Ki, and S. M. Shin, "Isorhamnetin Inhibits Reactive Oxygen Species-Dependent Hypoxia Inducible Factor (HIF) -1 α Accumulation," vol. 39, no. 11, pp. 1830–1838, 2016.
78 Y. Liu, S. Xie, Y. Wang, K. Luo, Y. Wang, and Y. Cai, "Liquiritigenin Inhibits Tumor Growth and Vascularization in a Mouse Model of Hela Cells," pp. 7206–7216, 2012, doi: 10.3390/molecules17067206.
79 Z. Wang et al., "Dietary Compound Isoliquiritigenin Inhibits Breast Cancer Neoangiogenesis via VEGF / VEGFR-2 Signaling Pathway," vol. 8, no. 7, 2013, doi: 10.1371/journal.pone.0068566.
80 M. Motallebi et al., "Naringenin: A potential flavonoid phytochemical for cancer therapy," Life Sci., vol. 305, p. 120752, 2022, doi: https://doi.org/10.1016/j.lfs.2022.120752.
[81 H. Li et al., "Naringin inhibits growth potential of human triple-negative breast cancer cells by targeting β-catenin signaling pathway," Toxicol. Lett., vol. 220, no. 3, pp. 219–228, 2013, doi: https://doi.org/10.1016/j.toxlet.2013.05.006.
82 N. Song et al., "Naringin promotes fracture healing through stimulation of angiogenesis by regulating the VEGF/VEGFR-2 signaling pathway in osteoporotic rats," Chem. Biol. Interact., vol. 261, pp. 11–17, 2017, doi: https://doi.org/10.1016/j.cbi.2016.10.020.
83 H. Zalpoor, M. Bakhtiyari, H. Shapourian, P. Rostampour,

C. Tavakol, and M. Nabi-Afjadi, "Hesperetin as an anti-SARS-CoV-2 agent can inhibit COVID-19-associated cancer progression by suppressing intracellular signaling pathways," Inflammopharmacology, vol. 30, no. 5, pp. 1533–1539, 2022, doi: 10.1007/s10787-022-01054-3.

84 D. Stanisic, A. F. Costa, W. J. Favaro, L. Tasic, A. B. Seabra, and N. Duran, "Anticancer Activities of Hesperidin and Hesperetin In vivo and their Potentiality against Bladder Cancer," J. Nanomed. Nanotechnol., vol. 09, no. 05, 2018, doi: 10.4172/2157-7439.1000515.

85 S. Jain and A. Vaidya, "Comprehensive review on pharmacological effects and mechanism of actions of taxifolin: A bioactive flavonoid," Pharmacol. Res. - Mod. Chinese Med., vol. 7, p. 100240, 2023, doi: https://doi.org/10.1016/j.prmcm.2023.100240.

86 S. S. Butt, K. Khan, Y. Badshah, M. Rafiq, and M. Shabbir, "Evaluation of pro-apoptotic potential of taxifolin against liver cancer," PeerJ, vol. 9, pp. 1–20, 2021, doi: 10.7717/peerj.11276.

87 Z. Wang et al., "Bioactivity-Guided Identification and Cell Signaling Technology to Delineate the Lactate Dehydrogenase A Inhibition Effects of Spatholobus suberectus on Breast Cancer," PLoS One, vol. 8, no. 2, 2013, doi: 10.1371/journal.pone.0056631.

88 Y. Cheng, X. Li, M.-Y. Fang, Q.-J. Ye, Z.-M. Li, and G. J. Ahammed, "Systemic H2O2 signaling mediates epigallocatechin-3-gallate-induced cadmium tolerance in tomato," J. Hazard. Mater., vol. 438, p. 129511, 2022, doi: https://doi.org/10.1016/j.jhazmat.2022.129511.

89 Q. Zhang, X. Tang, Q. Lu, Z. Zhang, J. Rao, and A. D. Le, "Green tea extract and (À) -epigallocatechin-3-gallate inhibit hypoxia- and serum-induced HIF-1 A protein accumulation and VEGF expression in human cervical carcinoma and hepatoma cells," vol. 5, no. May, pp. 1227–1239, 2006, doi: 10.1158/1535-7163.MCT-05-0490.

90 H. Wang, S. Bian, and C. S. Yang, "Green tea polyphenol EGCG suppresses lung cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1α," Carcinogenesis, vol. 32, no. 12, pp. 1881–1889, 2011, doi: 10.1093/carcin/bgr218.

91 Y. Zhang et al., "Dietary compound proanthocyanidins from Chinese bayberry (Myrica rubra Sieb. et Zucc.) leaves inhibit angiogenesis and regulate cell cycle of cisplatin-resistant ovarian cancer cells via targeting Akt pathway," J. Funct. Foods, vol. 40, pp. 573–581, 2018, doi: https://doi.org/10.1016/j.jff.2017.11.045.

92 Y. Gao, G. O. Rankin, Y. Tu, and Y. C. Chen, "Theaflavin-3 , 3 ' -digallate decreases human ovarian carcinoma OVCAR-3 cell-induced angiogenesis via Akt and Notch-1 pathways , not via MAPK pathways," pp. 281–292, 2016, doi: 10.3892/ijo.2015.3257.

93 A. P. G. da Silva, S. Zia, O. D. John, M. C. de Souza, L. C. da Silva, and W. G. Sganzela, "Delphinidin: Sources, Biosynthesis, Bioavailability, Bioactivity, and Pharmacology BT - Handbook of Dietary Flavonoids," J. Xiao, Ed., Cham: Springer International Publishing, 2023, pp. 1–31. doi: 10.1007/978-3-030-94753-8_56-1.

94 M. H. Kim et al., "Delphinidin inhibits angiogenesis through the suppression of HIF-1α and VEGF expression in A549 lung cancer cells," Oncol. Rep., vol. 37, no. 2, pp. 777–784, 2017, doi: 10.3892/or.2016.5296.

95 A. Sarfraz et al., "Biochanin A: A novel bioactive multifunctional compound from nature," Sci. Total Environ., vol. 722, p. 137907, 2020, doi: https://doi.org/10.1016/j.scitotenv.2020.137907.

96 A. Jain, J. C. K. Lai, and A. Bhushan, "Biochanin A inhibits endothelial cell functions and proangiogenic pathways: implications in glioma therapy," Anticancer. Drugs, vol. 26, no. 3, 2015.

97 Z. Y. Lin, Q. Z. Yun, L. Wu, T. W. Zhang, and T. Z. Yao, "Pharmacological basis and new insights of deguelin concerning its anticancer effects," Pharmacol. Res., vol. 174, p. 105935, 2021, doi: https://doi.org/10.1016/j.phrs.2021.105935.

98 S. H. Oh et al., "Identification of novel antiangiogenic anticancer activities of deguelin targeting hypoxia-inducible factor-1 alpha," Int. J. Cancer, vol. 122, no. 1, pp. 5–14, 2008, doi: 10.1002/ijc.23075.

99 V. Singh-Gupta et al., "Daidzein effect on hormone refractory prostate cancer in vitro and in vivo compared to genistein and soy extract: Potentiation of radiotherapy," Pharm. Res., vol. 27, no. 6, pp. 1115–1127, 2010, doi: 10.1007/s11095-010-0107-9.

100 V. Singh-Gupta et al., "Radiation-induced HIF-1α cell survival pathway is inhibited by soy isoflavones in prostate cancer cells," Int. J. Cancer, vol. 124, no. 7, pp. 1675–1684, 2009, doi: 10.1002/ijc.24015.

101 Y. Liu, C. K. Veena, J. B. Morgan, K. A. Mohammed, M. B. Jekabsons, and D. G. Nagle, "Methylalpinumisoflavone Inhibits Hypoxia-inducible Factor-1 (HIF-1) Activation by Simultaneously Targeting Multiple Pathways * □," J. Biol. Chem., vol. 284, no. 9, pp. 5859–5868, 2009, doi: 10.1074/jbc.M806744200.