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Antiangiogenic role of natural flavonoids and their molecular mechanism: an update

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Abstract

Background: Angiogenesis is the development of new blood vessels from the existing vasculature, which is important in normal developmental processes. Angiogenesis is a key step in tumor growth, invasion, and metastasis. Angiogenesis is necessary for the proper nourishment and removal of metabolic wastes from tumor sites. Therefore, modulation of angiogenesis is considered a therapeutic strategy of great importance for human health.

Main body: Numerous bioactive plant compounds are recently tested for their antiangiogenic potential. Among the most frequently studied are flavonoids which are abundantly present in fruits and vegetables. Flavonoids inhibit angiogenesis and metastasis through the regulation of multiple signaling pathways. Flavonoids regulate the expression of VEGF, matrix metalloproteinases (MMPs), EGFR, and inhibit NFB, PI3-K/Akt, and ERK1/2 signaling pathways, thereby causing strong antiangiogenic effects. This present review aimed to provide up-to-date information on the molecular mechanisms of antiangiogenic properties of natural flavonoids.

Conclusion: Presently developed antiangiogenic drugs in malignant growth treatment do not meet assumptions about adequacy and safety. So further investigations are needed in this field in the future. More recently, flavonoids are the most effective antiangiogenic agent, by inhibition of signaling pathways.

Keywords: Angiogenesis, Vascular endothelial growth factor, Matrix metalloproteinases, Flavonoids, Metastasis

Background

Polyphenols which are the bioactive compounds derived from natural resources have pulled in a lot of consideration for their well-being advancing impacts. Flavonoids are a significant class of secondary metabolites having a polyphenolic structure, commonly found in natural sources such as vegetables, fruits, and certain refreshments (Table 1) [22]. They have a variety of useful antioxidant and biochemical consequences related to different infections, for example, carcinoma, Alzheimer's problem, and atherosclerosis, among others [23–25]. Flavonoids have various medicinal features such as anti-inflammatory, neuroprotective, and cardioprotective [26–28] activities. A few previous studies showed flavonoids have antiviral and antibacterial properties [29–31]. Furthermore, there are a lot of articles that zeroed on the anticancer properties of phenolics [32–34]. As of now, flavonoids and their subordinates have been seriously assessed corresponding to malignant growth cell control as well as endothelial cell and angiogenic controllers.

The compounds of flavonoids are present in nature and found in various parts of the plant. Plants used flavonoids for their development and protection oppose plaque [35]. Several flavonoids are simply recognized as pigments of flowers in the majority of families of angiosperm [36]. Flavonoids have numerous subclasses which consisted of flavones, chalcones, isoflavones, and flavonols.

Flavonoids can be classified into different subgroups depending on the carbon of the C ring on which the B

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Table 1 Angiogenic effect of flavonoids and their molecular mechanisms. ↓ inhibit or decrease of expression, secretion, or activity; ↑ increase of expression, secretion, or activity

S. no	Name of flavonoid	Sources	In vitro/ in vivo	Mechanism of action	References
1	Naringenin	Tomatoes, oranges	HUVEC	VEGF/KDR signaling pathway ↓	Chen et al. [1]; Li et al. [2]
2	Kaempferol	Vegetables, tea, and natural products	HUVEC; SCC-4 cells; Zebrafish	↓ VEGFR2; PI3K/AKT, MEK and ERK signaling pathways ↓; MMP-2 ↓; AP-1 action ↓; ERK1/2 phosphorylation ↓; eNOS ↓	Hu et al. [3], Chin HK et al. [4]
3	Chrysin	Honey, propolis, and passion flowers	Rat model	↓ VEGF; HIF-1 ↓	Song et al. [5]
4	Myricetin	Vegetables, fruits, nuts, berries, and herbs	CAM assay, HUVEC	↓ VEGF-A; Incite ROS-intervened apoptosis; PI3K/Akt/mTOR signaling pathways ↓; VEGFR2 and p38MAPK ↓	Zhou et al. [6], Kim et al. [7], Santosh et al. [8]
5	Luteolin	Celery, broccoli, apples, and carrots	HRMECs, HUVECs, Hs-746T cells	↓ VEGF; HIF-1α ↓; VEGFR2 ↓; MMP-1 and MMP-9 ↓; Notch1 expression ↓; P-Akt ↓	Zang et al. [9], Pervin et al. [10], Park et al. [11]
6	Epigallocatechin 3 gallate, Y6	Tea, green, white, and black teas	Renal carcinoma cells; HUVECs	MMP-2 and MMP-9 ↓; Endoglin/smad1signaling pathways ↓; VEGF ↓; ERK1/2 /MAPK, AKT/PI3K/VEGF/ HIF-α pathways ↓	Liao et al. [12], Chen et al. [13], Chen et al. [14]
7	Nobiletin	Citrus peels	Human Dermal Fibroblasts	MMP-9 ↓; p38MAPK activity ↓	Kim et al. [15]
8	Wogonin	*Scutelleria biacalensis*	HePG2	MMP-9 ↓	Hong et al. [16]
9	Hesperidin	Citrus fruits	Mice	MMP-9 ↓; mitogen MAPK ↓	Lee et al. [17]
10	Oroxyloside	*Oroxylum indicum, Scutellaria baicalensis*	EA.hy926 cells	Akt/MAPK/NF-κB signaling pathways ↓; VEGFR2 ↓	Zhao et al. [18]
11	Herbacetin	*Rhodiola rosea*	Hs294T, A375 cells	EGFR-ERK/AKT signaling pathways ↓; MMP-9 ↓	Li et al. [19]
12	Delphinidin	Fruits, flowers, and leaves of plants	A549 cells	HIF-1 ↓; ERK/P13K/Akt/mTOR/p70S6K signaling pathways ↓	Kim et al. [20]
13	Quercetin	Vegetables and fruits	Human retinal endothelial cells	↓ VEGFR2; MEK/ERK, PI3K/AKT, MEK/JNK signaling pathways ↓	Lupo et al. [21]

ring is bound and the degree of oxidation and unsaturation of the C ring. The third position where the C ring is linked with the B ring is known as flavonoids isoflavones. The fourth position where the C ring is linked with the B ring is known as neoflavonoids. The second position where the C ring is linked with the B ring can be divided into various groups such as flavonols, flavones, flavanonols, catechins, anthocyanins, and chalcone (Fig. 1) [38].

Angiogenesis is the generation of fresh blood vessels from a prior vasculature [39]. Angiogenesis is fundamental for the development and revival of tissue where it is favorable for a lot of progress including wound healing and embryogenesis [40]. Angiogenesis regulation is difficult and is sustained by the stability within endogenous stimulators (hypoxia-inducible factors (HIFs), platelet-derived growth factors (PDGFs), and vascular endothelial growth factors (VEGF)) and inhibitors (endostatin and angiostatin). Subsequently, focusing on angiogenesis has been a helpful methodology for the treatment of various infections. Unregulated angiogenesis may bring about various pathologies [41], for example, diabetic retinopathy [42], rheumatoid joint pain [43], psoriasis, disease development [44], and adolescent hemangiomas [45]. Tumor development and metastasis are angiogenesis subordinates [46]. A developing tumor needs a wide organization of vessels to flexibly supplement oxygen. Furthermore, the new intratumoral veins provide a route for tumor cells to enter the path and to metastasize to far-off organs. Subsequently, every organ framework may include sicknesses in which angiogenesis is a significant factor.

A few previous investigations, either in vivo or in vitro, archived the anticancer capability of phenolic substances. Phytochemicals that block some key steps in tumorigenesis have been accounted for [47]. Phytochemicals may incorporate interruption of cancer-causing agent actuation and expanded cancer-causing agent detoxication [48], the balance of flagging pathways [49, 50], focusing on disease foundational microorganisms [51], apoptosis enlistment [52], or acceptance of cell cycle arrest [53, 54]. Besides, polyphenolic substances were additionally reported to adjust several phases in angiogenesis, for example, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF); or hypoxia-inducible factor-1α (HIF-1α) [55], matrix metalloproteinase (MMP) action [56], or endothelial cell multiplication and movement [57].

The present literature review article explains the up-to-date information about the molecular mechanism of flavonoids and their antiangiogenic properties.

Main text

Flavonoids' impact on different pathways

Impact on signaling pathways

Intercellular correspondence assumes a key part in the control of cell exercises just as in the association of all cell activities. Signaling communication unbalance can

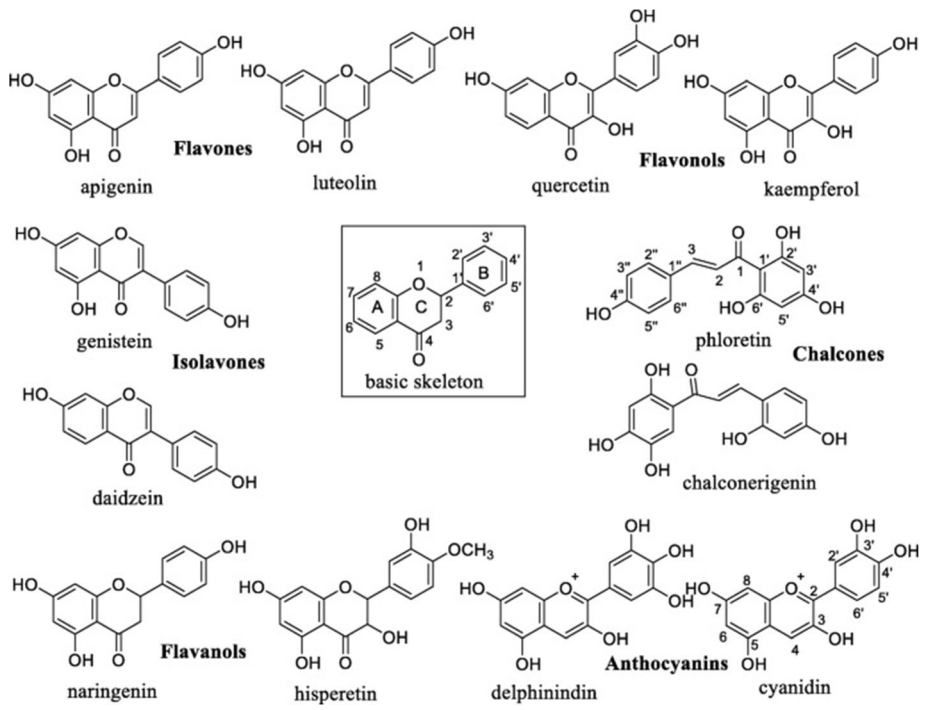

Fig. 1 Chemical structure of flavonoids and their classes [37]

prompt a wide range of obsessive states, inclusive of most cancers and strange tumorigenesis [58]. Hence, focusing on signaling pathways has become a great technique to combat tumorigenesis.

VEGF signaling pathway

Vascular endothelial development factor is a significant supporter of angiogenic factor, applying its cell impacts essentially through the stimulation of vascular endothelial growth factor receptor 1, vascular endothelial growth factor receptor 2, and two tyrosine kinase receptors. The important VEGF receptor on the endothelial surface is VEGFR2. Vascular endothelial growth factor receptor 2 is the principal VEGF receptor on the endothelial cell surface [59]. Not many examinations revealed the significant role of VEGFR2 in lump neovascularization, metastasis, and development [60]. Actuation of VEGFR2 prompts different downstream signals of phosphorylation, for example, p38 mitogen-activated protein kinases (p38MAPK), phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase-1, 2 (ERK 1/2), and AK tymoma protein (AKT), trailed through the initiation of endothelial cells (e.g., multiplication, relocation) [61].

bFGF signaling pathway

Basic fibroblast growth factors are a group of pleiotropic aspects associated with the guideline of different major measures, as well as cell expansion, separation, survival, and angiogenesis [62]. It can also stimulate endothelial cell receptors or actuate the proangiogenic arrivals from different types of cells with ensuing angiogenesis stimulation [63]. In addition, it appears to be that downregulating of bFGF flagging can be associated with protection from VEGF-inhibitor treatment [64]. Presently, in clinical investigations, different types of molecules came to be revealed to interfere with the FGFR/FGF axis [65].

HIF-1 signaling pathway

The significant controller of oxygen homeostasis in cells presented to hypoxia is HIF-1. This is associated with a wide range of capacities, for example, irritation, cell endurance, and apoptosis [66]. In different types of tumors, hypoxia is a usual component and assumes a HIF-1 key part in the variation of cells to reduce oxygen stress [67]. It can trigger the statement of various supportive factors of angiogenesis, as well as VEGF and its receptors, angiopoietins 1 and 2, platelet-determined development factor, plasminogen activator inhibitor-1, the angiopoietin receptor TIE-2, MMP-2, and MMP-9 [68].

Impact of flavonoids on matrix metalloproteinases

A vascular cellar layer is needed to advance endothelial cell intrusion into the interstitial matrix. This cycle is carried out by MMPs which are also known as proteolytic proteins. As was illustrated, MMP-9 and MMP-2 assume a significant part of angiogenic growth [69]. Several flavonoids were demonstrated to hinder the movement of various MMPs, and it is recommended that this impact may add to their antiangiogenic/anticancer impact.

Molecular mechanism of flavonoids

Naringenin is a type of flavonoid which is abundantly found in tomatoes and oranges. Naringenin has possessed some biological activities like hypolipidemic, hypocholesterolemic, and antagonistic to estrogenic; antihypertensive; and anti-inflammatory exercises. Qunyi et al. [2] reported the antiangiogenic role of naringenin in HUVEC cell lines. The authors revealed that naringenin slowed down a few stages in cell expansion, migration, cell cycle arrest, apoptosis, and tube development of endothelial cells. These impacts were joined by the VEGF inhibition initiated by the intervening of the VEGF/KDR pathway (Fig. 1) [2]. Afterward, Chen et al. [1] reported the antiangiogenic activity of naringenin in HUVEEC and zebrafish. They revealed that naringenin showed potential antiangiogenic activity by inhibiting SIV formation in zebrafish embryos [1].

Kaempferol is a flavonoid that is abundantly found in vegetables, tea, and natural products [70], was additionally found to weaken malignancy neovascularization through interruption of VEGF discharge in human cancer cell lines [71]. Chin et al. [4] studied the antiangiogenic activity of kaempferol in HUVEC cell lines. They revealed that kaempferol fundamentally reduced the VEGF-stimulated HUVEC suitability. Kaempferol set off antiangiogenic action in VEGF-stimulated HUVECs by reducing the VEGFR 2 protein level and kinase action. In addition, they found that kaempferol restrains angiogenic capacity by focusing on VEGF receptor-2, and downregulating the PI3K/AKT, MEK, and ERK pathways in VEGF-stimulated HUVECs (Fig. 2) [4]. Later Hu W-H et al. [3] studied the antiangiogenic activity of kaempferol in endothelial cells. They strongly revealed that kaempferol potentiated the extracellular signal-regulated kinase (Erk), endothelial nitric oxide synthase (eNOS), and VEFGR2 phosphorylation [3].

Chrysin is a flavonoid that is abundantly found in honey, propolis, and passion flowers. Although, accurate mechanisms underlying the biological activities of chrysin are still unknown. Song et al. [5] studied the

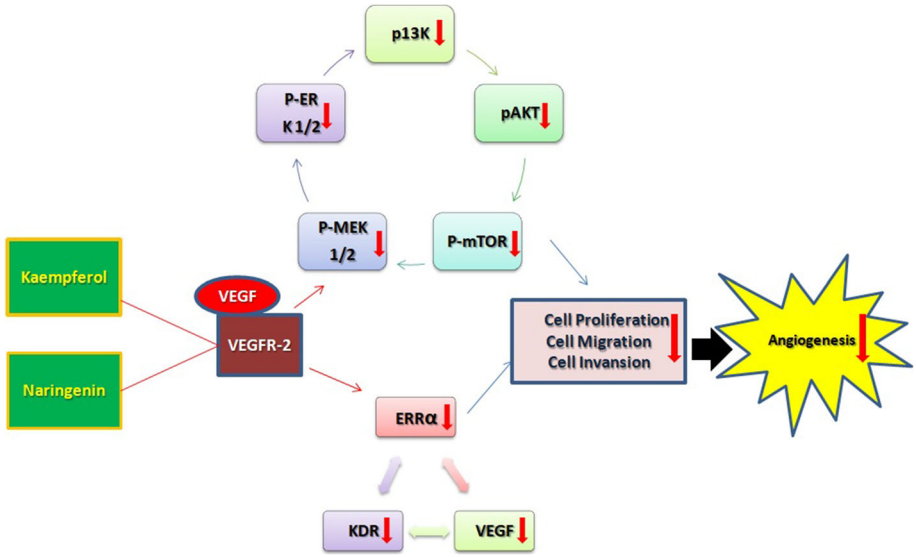

Fig. 2 A representation describing the molecular mechanism of kaempferol and naringenin on the antiangiogenic activity in HUVEC cells

antiangiogenic activity of chrysin in rat models. They revealed that chrysin significantly reduced VEGF and HIF-α expression levels [5].

Myricetin is a flavonoid that is abundantly found in vegetables, fruits, nuts, berries, and herbs. Santosh et al. [8] studied the antiangiogenic activity of myricetin in HUVECs and CAM assay. They revealed that myricetin repressed the development of freshly structured veins in chicken embryonic organisms and downregulated the outflow of VEGF-A [8]. Later, Kim et al. [7] studied the antiangiogenic activity of myricetin using HUVEC cell lines. They revealed that myricetin significantly reduced angiogenesis by inhibiting signal pathways such as Akt/PI3K/mTOR [7]. Zhou et al. [6] studied the antiangiogenic activity of myricetin. They revealed that myricetin significantly reduced angiogenesis by inhibiting P38K signaling pathway and VEGF/VEGFR2 expression levels [6].

Luteolin is a flavonoid which is abundantly found in natural sources such as celery, broccoli, apples, and carrots. Previous reports showed that luteolin possesses an antiangiogenic activity in different endothelial cells. Sung Wook Park et al. [11] reported the antiangiogenic activity of luteolin in HRMECs. They revealed that luteolin inhibited angiogenesis in HRMECs by reducing VEGF expression through the HIF-1α subordinate system by a blockage of ROS production, and VEGF-induced angiogenesis through managing possibly VEGFR2 signaling pathway [11]. Monira et al. [10] revealed that luteolin suppresses the expression of MMP-1 and MMP-9 genes in UVA and UVB-uncovered human dermal fibroblast cells. Zang et al. [9] studied the antiangiogenic activity of luteolin in gastric cancer. They revealed that luteolin significantly reduced angiogenesis by inhibiting the secretion of VEGF through Notch 1 expression [9].

Epigallocatechin 3 gallate is a flavonoid which is abundantly found in tea, green, white, and black teas. Chen et al. [14] studied the antiangiogenic activity of Epigallocatechin 3 gallate, and they revealed that Epigallocatechin 3 gallate had the option to inhibit the relocation and attack of RCC cells by downregulating MMP-9 and MMP-2. Chen et al. [13] studied the role of antiangiogenesis using Epigallocatechin 3 gallate in HUVEC cell lines. They revealed that EGCG decreased angiogenesis by inhibiting the VEGF, endoglin/smad1 signaling pathways (Fig. 3) [13]. Liao et al. [12] studied the antiangiogenic activity of EGCG in hepatocellular carcinoma. They revealed that EGCG significantly decreased angiogenesis by inhibiting the pathways such as PI3K/AKT/HIF-α/VEGF and ERK1/2 /MAPK [12].

Wogonin is a flavonoid which is abundantly found in Radix Scutellariae, a notable natural agent which has indicated striking anticarcinogenic and chemopreventive limit in different examinations [72–74]. Ming Hong et al. [16] reported that wogonin suppresses the action of matrix metalloproteinase-9 and inhibits migration and attack in human hepatocellular carcinoma.

Nobiletin is a flavonoid that is abundantly found in citrus peels. Kim et al. [15] studied the MMP-9

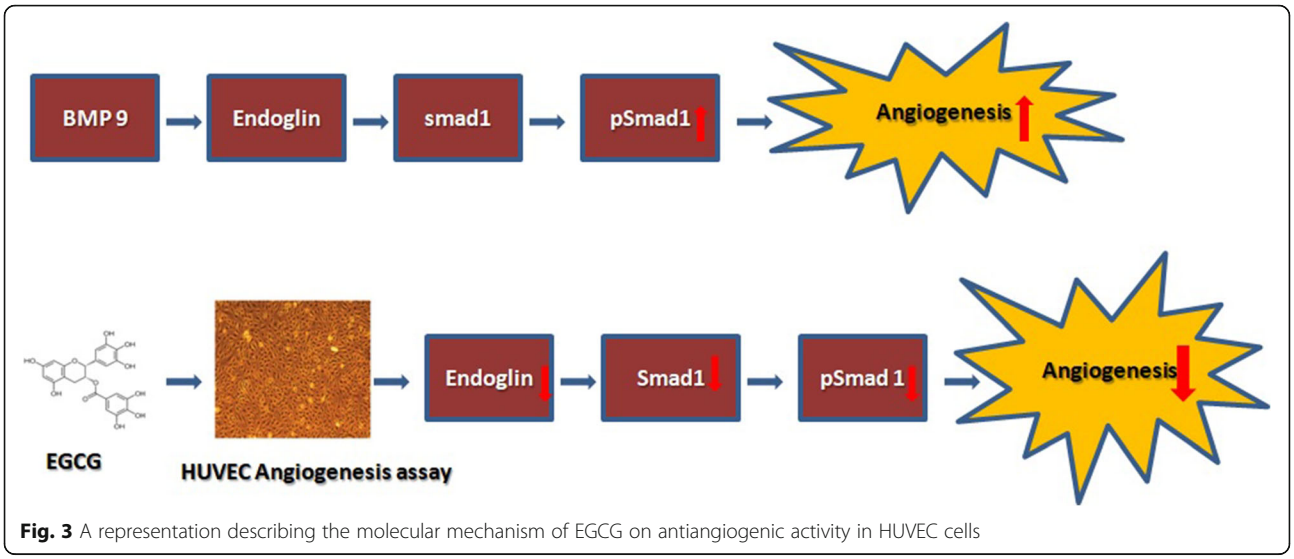

Fig. 3 A representation describing the molecular mechanism of EGCG on antiangiogenic activity in HUVEC cells

expression in human dermal fibroblasts. They revealed that nobiletin suppresses the MMP-9 expression under PMA stimulation, through the regulation of p38MAPK activity [15].

Lin et al. [75] reported that kaempferol inhibits AP-1 action, decreases MMP-2 expression, and consequently suppresses the interference of SCC4 cells and reveals that kaempferol inhibits ERK1/2 phosphorylation, successfully prompting MMP-2 downregulation [75].

Hesperidin is a flavonoid which is abundantly found in citrus fruits. Lee et al. [17] reported that the flavonoid hesperidin applies an anti-photoaging impact by downregulating MMP-9 expressions through mitogen MAPK-dependent signaling pathways.

Oroxyloside is a flavonoid which is abundantly found in *Oroxylum indicum* and *Scutellaria baicalensis*. Zhao et al. [18] demonstrated the antiangiogenic effects of oroxyloside. They reported that oroxyloside inhibited angiogenesis by downregulating the Akt/MAPK/NF-κB pathways. Furthermore, they revealed that oroxyloside exhibited suppression of VEGFR2 through in vivo assays (Fig. 4) [18].

Herbacetin is a flavonoid which is abundantly found in *Rhodiola rosea*. Li et al. [19] demonstrated the antiangiogenic activity of herbacetin. They revealed that herbacetin suppressed tumor growth both in vivo and in vitro. Furthermore, they confirmed that herbacetin inhibited tumor angiogenesis by blocking the EGFR-ERK/AKT-MMP-9 signaling pathway (Fig. 5) [19].

Delphinidin is a flavonoid which is abundantly found in fruits, flowers, and leaves of plants. Kim et al. [7] reported the antiangiogenic activity of delphinidin. They found that delphinidin decreases the expression level of HIF-1, which is a VEGF transcription factor. They also revealed that it decreases the HIF-1 expression by blocking the ERK and PI3K/Akt/mTOR/p70S6K signaling pathways (Fig. 6) [20].

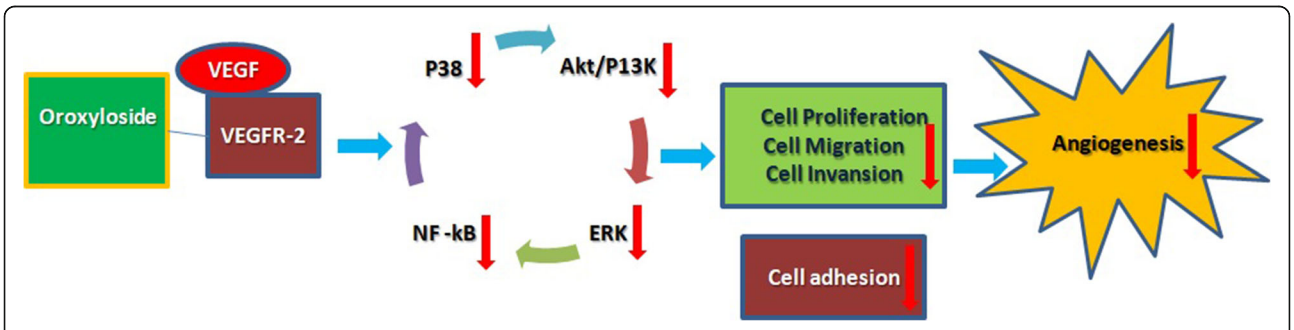

Fig. 4 A graphical representation describing the molecular mechanism of oroxyloside on the antiangiogenic activity in EA.hy926 cells

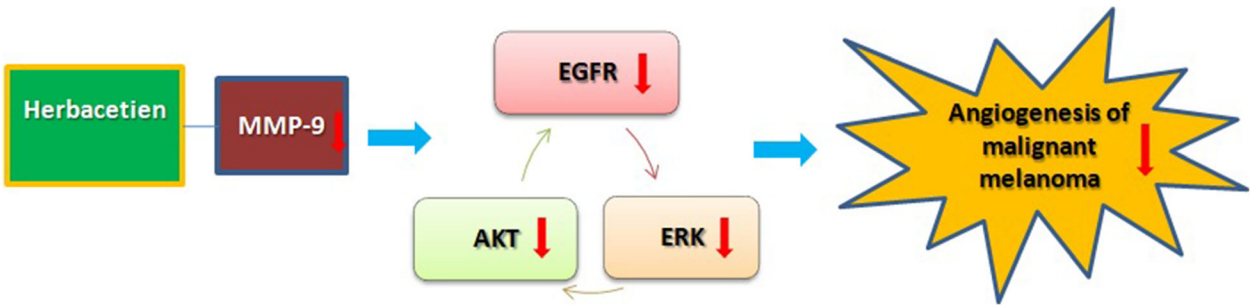

Fig. 5 A graphical representation describing the molecular mechanism of Herbacetien on the antiangiogenic activity in HUVEC cells

Quercetin is a flavonoid which is abundantly found in vegetables and fruits. Lupo et al. [21] studied the antiangiogenic activity of quercetin in HRE cells. They revealed that quercetin decreases angiogenesis by inhibiting the signaling pathways VEGFR2, MEK/ERK, PI3K/AKT, and MEK/JNK [21].

Conclusion

Pharmacological examinations carried out on a few flavonoids in vitro and in vivo tests confirmed that their antiangiogenic impact is mediated through a huge variety of cellular and molecular functions. Every individual substance of these gatherings can be assessed as a multi-target controller, affecting different segments in various cell transduction pathways.

In conclusion, the data present in the review established the molecular mechanisms of different flavonoids. The present review gave generous details that will highlight advanced examinations by dealing with the existing gaps in the literature concerning the different flavonoids' antiangiogenic activity and the prominence of their upcoming possible therapeutically effective antiangiogenic agents.

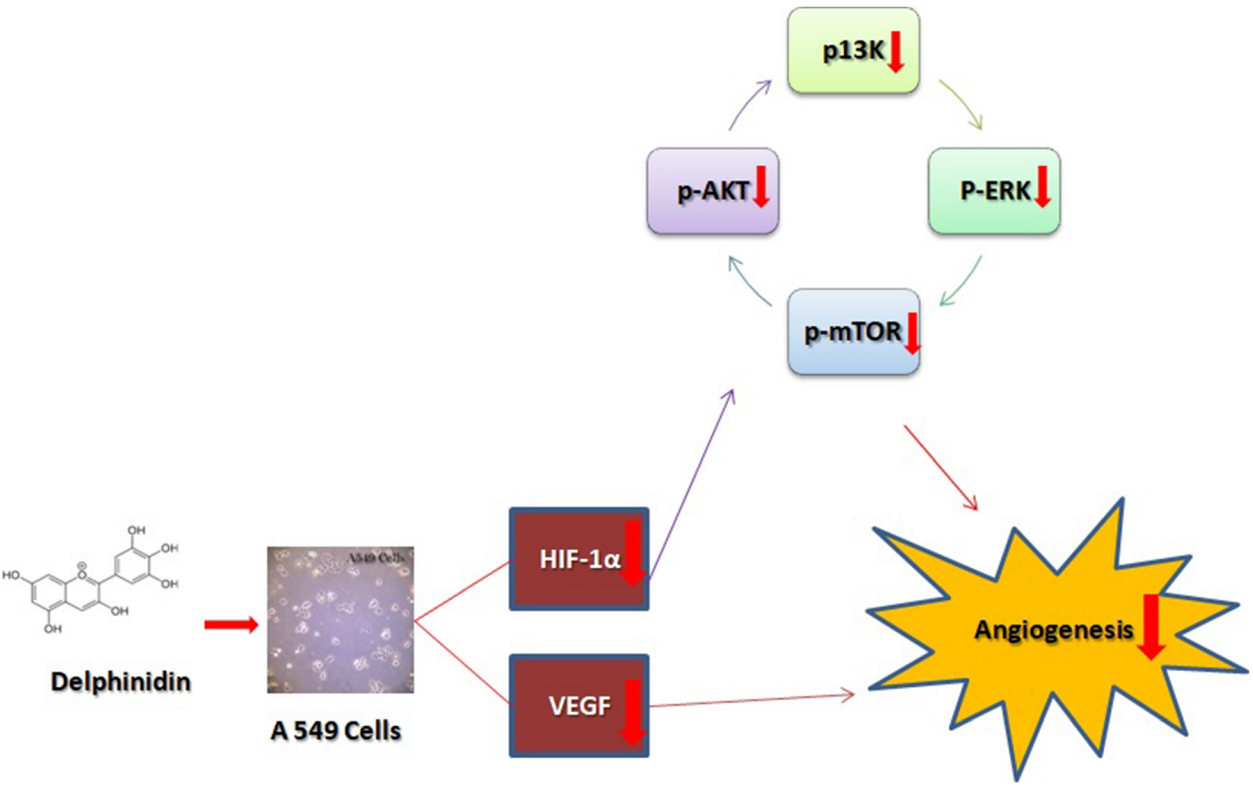

Fig. 6 A representation describing the molecular mechanism of delphinidin on the antiangiogenic activity in A 549 cells

Abbreviations
VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; bFGF: Basic fibroblast growth factor; HIF-1α: Hypoxia-inducible factor-1α; MMP: Matrix metalloproteinases; HUVEC: Human umbilical cord vascular endothelial cells; EGFR: Epidermal growth factor receptor; Akt: AK tymoma protein; Erk 1/2: Extracellular signal-regulated kinase-1, 2; eNOS: Endothelial nitric oxide synthase; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light chain enhancer of activated B cells; PI3K: Phosphatidylinositol 3-kinase; JNK: c-Jun-N-terminal kinase p; P 70S6K: Ribosomal protein S6 kinase beta-1; KDR: Kinase insert domain-containing receptor

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Authors' contributions
The first author (SK) collected the data from articles and drafted the manuscript. GK revised and did the final approval of the draft of the manuscript. LK contributed to drafting the manuscript. All the authors have read and approved the manuscript for the submission.

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Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
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Competing interests
All the authors declare that they have no competing interests.

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References

1. Chen L, Yang B, Tang B, Gong G, Kam H, Gao C et al (2018) Differential angiogenic activities of naringin and naringenin in zebrafish in vivo and human umbilical vein endothelial cells in vitro. Journal of Functional Foods 49:369–377. https://doi.org/10.1016/j.jff.2018.08.010
2. Li Q, Wang Y, Zhang L, Chen L, Du Y, Ye T, Shi X et al (2016) Naringenin exerts anti-angiogenic effects in human endothelial cells: iInvolvement of ERRα/VEGF/KDR signaling pathway. Fitoterapia. 111:78–86. https://doi.org/10.1016/j.fitote.2016.04.015
3. Hu WH, Wang HY, Xia YT, Dai DK, Xiong QP, Dong TTX, Duan R, Chan GKL, Qin QW, Tsim KWK (2020) Kaempferol, a major flavonoid in ginkgo folium, potentiates angiogenic functions in cultured endothelial cells by binding to vascular endothelial growth factor. Frontiers in pharmacology. 11:526. https://doi.org/10.3389/fphar.2020.00526
4. Chin HK, Horng CT, Liu YS, Lu CC, Su CY, Chen PS, Chiu HY, Tsai FJ, Shieh PC, Yang JS, Yang JS et al (2018) Kaempferol inhibits angiogenic ability by targeting VEGF receptor-2 and downregulating the PI3K/AKT, MEK and ERK pathways in VEGF-stimulated human umbilical vein endothelial cells. Oncol Rep 39(5):2351–2357. https://doi.org/10.3892/or.2018.6312
5. Song JH, Moon KY, Lee SC, Kim SS et al (2020) Inhibition of hypoxia-inducible factor-1α and vascular endothelial growth factor by chrysin in a rat model of choroidal neovascularization. Int J Mol Sci. 21(8):2842. https://doi.org/10.3390/ijms21082842
6. Zhou Z, Mao W, Li Y, Qi C, He Y (2019) Myricetin inhibits breast tumor growth and angiogenesis by regulating VEGF/VEGFR2 and p38MAPK signaling pathways. The Anatomical Record. 302(12):2186–2192. https://doi.org/10.1002/ar.24222
7. Kim GD et al (2017) Myricetin inhibits angiogenesis by inducing apoptosis and suppressing PI3K/Akt/mTOR signaling in endothelial cells. J Cancer Prev. 22(4):219–227. https://doi.org/10.15430/JCP.2017.22.4.219
8. Santosh W et al (2014) Anti-angiogenic activity of natural flavonoid myricetin on chick chorioallantoic membrane (cam) in-vivo. Int J Pharmacy. 4:160–165
9. Zang M, Hu L, Zhang B, Zhu Z, Li J, Zhu Z, Yan M, Liu B (2017) Luteolin suppresses angiogenesis and vasculogenic mimicry formation through inhibiting Notch1-VEGF signaling in gastric cancer. Biochemical and biophysical research communications. 490(3):913–919. https://doi.org/10.1016/j.bbrc.2017.06.140
10. Pervin M, Unno K, Nakamura Y, Imai S et al (2016) Luteolin suppresses ultraviolet A- and B-induced matrix metalloproteinase 1- and 9 expression in human dermal fibroblast cells. J Nutr Food Sci. 6:560
11. Park SW, Cho CS, Jun HO, Ryu NH, Kim JH, Yu YS, Kim JS, Kim JH et al (2012) Anti-angiogenic effect of luteolin on retinal neovascularization via blockade of reactive oxygen species production. Invest Ophthalmol Vis Sci. 53(12):7718–7726. https://doi.org/10.1167/iovs.11-8790
12. Liao ZH, Zhu HQ, Chen YY, Chen RL, Fu LX, Li L, Zhou H, Zhou JL, Liang G (2020) The epigallocatechin gallate derivative Y6 inhibits human hepatocellular carcinoma by inhibiting angiogenesis in MAPK/ERK1/2 and PI3K/AKT/HIF-1α/VEGF dependent pathways. J Ethnopharmacol. 259:112852. https://doi.org/10.1016/j.jep.2020.112852
13. Chen CY, Lin YJ, Wang CC, Lan YH, Lan SJ, Sheu MJ (2019) Epigallocatechin-3-gallate inhibits tumor angiogenesis: involvement of endoglin/Smad1 signaling in human umbilical vein endothelium cells. Biomed Pharmacotherapy. 120:109491. https://doi.org/10.1016/j.biopha.2019.109491
14. Chen SJ, Yao XD, Peng BO et al (2016) Epigallocatechin-3-gallate inhibits migration and invasion of human renal carcinoma cells by downregulating matrix metalloproteinase-2 and matrix metalloproteinase-9. Exp There Med. 11(4):1243–1248. https://doi.org/10.3892/etm.2016.3050
15. Kim JJ, Korm S, Kim WS, Kim OS, Lee JS, Min HG, Chin YW, Cha HJ et al (2014) Nobiletin suppresses MMP-9 expression through modulation of p38 MAPK activity in human dermal fibrobalsts. Biol Pharm Bull. 37(1):158–163. https://doi.org/10.1248/bpb.b13-00534
16. Hong M, Cheng H, Song L, Wang W, Wang Q, Xu D, Xing W (2018) Wogonin suppresses the activity of matrix metalloproteinase-9 and inhibits migration and invasion in human hepatocellular carcinoma. Molecules. 23(2):384. https://doi.org/10.3390/molecules23020384
17. Lee HJ, Im A-R, Kim S-M, Kang H-S, Lee JD, Chae S (2018) The flavonoid hesperidin exerts anti-photoaging effect by downregulating matrix metalloproteinase (MMP)-9 expression via mitogen activated protein kinase (MAPK)-dependent signaling pathways. BMC complementary and alternative medicine vol. 18(1):39. https://doi.org/10.1186/s12906-017-2058-8
18. Zhao K, Li X, Lin B, Yang D, Zhou Y, Li Z, … Lu N et al (2017) Oroxyloside inhibits angiogenesis through suppressing internalization of VEGFR2/Flk-1 in endothelial cells. J Cell Physiol 233(4):3454–3464. https://doi.org/10.1002/jcp.26198 .
19. Li L, Fan P, Chou H, Li J, Wang K, Li H et al (2019) Herbacetin suppressed MMP9 mediated angiogenesis of malignant melanoma through blocking EGFR-ERK/AKT signaling pathway. Biochimie. 162:198–207. https://doi.org/10.1016/j.biochi.2019.05.003
20. Kim M-H, Jeong Y-J, Cho H-J, Hoe H-S, Park K-K, Park Y-Y et al (2016) Delphinidin inhibits angiogenesis through the suppression of HIF-1α and VEGF expression in A549 lung cancer cells. Oncology Reports. 37(2):777–784. https://doi.org/10.3892/or.2016.5296
21. Lupo G, Cambria MT, Olivieri M, Rocco C, Caporarello N, Longo A, Zanghì G, Salmeri M, Foti MC, Anfuso CD (2019) Anti-angiogenic effect of quercetin and its 8-methyl pentamethyl ether derivative in human microvascular endothelial cells. Journal of cellular and molecular medicine. 23(10):6565–6577. https://doi.org/10.1111/jcmm.14455

22. Panche AN, Diwan AD, Chandra SR et al (2016) Flavonoids: an overview. Journal of Nutritional Science. 5:e47. https://doi.org/10.1017/jns.2016.41
23. Burak M, Imen Y et al (1999) Flavonoids and their antioxidant properties. Turkiye Klin Tip Bil Derg 19:296–304
24. Ovando C, Hernandez D, Hernandez E et al (2009) Chemical studies of anthocyanins: a review. Food Chem 113(4):859–871. https://doi.org/10.1016/j.foodchem.2008.09.001
25. Lee Y, Yuk D, Lee J et al (2009) Epigallocatechin-3-gallate prevents lipopolysaccharide-induced elevation of β-amyloid generation and memory deficiency. Brain Res. 1250:164–174. https://doi.org/10.1016/j.brainres.2008.10.012
26. Peluso I, Raguzzini A, Serafini M (2013) Effect of flavonoids on circulating levels of TNF-α and IL-6 in humans: a systematic review and meta-analysis. Mol. Nutr. Food Res. 57(5):784–801. https://doi.org/10.1002/mnfr.201200721
27. Beking K, Vieira A (2010) Flavonoid intake and disability-adjusted life years due to Alzheimer's and related dementias: a population-based study involving twenty-three developed countries. Public Health Nutr. 13(9):1403–1409. https://doi.org/10.1017/S1368980009992990
28. Wang X., Ouyang Y.Y., Liu J., Zhao G (2014) Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Br. J. Nutr. 111:1–11, 1, 1, DOI: https://doi.org/10.1017/S000711451300278X.
29. Ben Lagha A, Haas B, Grenier D et al (2017) Tea polyphenols inhibit the growth and virulence properties of Fusobacterium nucleatum. Sci. Rep. 7(1): 44815. https://doi.org/10.1038/srep44815
30. Lee JH, Oh M, Seok JH, Kim S, Lee DB, Bae G, Bae HI, Bae SY, Hong YM, Kwon SO et al (2016) Antiviral effects of black raspberry (Rubus coreanus) seed and its gallic acid against influenza virus infection. Viruses. 8(6). https://doi.org/10.3390/v8060157
31. Su, X.; D'Souza, D.Het al (2013) Naturally occurring flavonoids against human norovirus surrogates. Food Environ. Virol. 5: 97–102, 2, DOI: https://doi.org/10.1007/s12560-013-9106-4
32. Hashemzaei M, Delarami Far A, Yari A, Heravi RE, Tabrizian K, Taghdisi SM, Sadegh SE, Tsarouhas K, Kouretas D, Tzanakakis G et al (2017) Anticancer and apoptosis inducing effects of quercetin in vitro and in vivo. Oncol. Rep. 38(2):819–828. https://doi.org/10.3892/or.2017.5766
33. Kubatka P, Kapinova A, Kello M, Kruzliak P, Kajo K, Vybohova D, Mahmood S, Murin R, Viera T, Mojzis J et al (2016) Fruit peel polyphenols demonstrate substantial anti-tumour effects in the model of breast cancer. Eur. J. Nutr. 55(3):955–965. https://doi.org/10.1007/s00394-015-0910-5
34. Secme M, Eroglu C, Dodurga Y, Bagci G et al (2016) Investigation of anticancer mechanism of oleuropein via cell cycle and apoptotic pathways in SH-SY5Y neuroblastoma cells. Gene. 585(1):93–99. https://doi.org/10.1016/j.gene.2016.03.038
35. Havsteen B (2002) The biochemistry and medical significance of the flavonoids. Pharmacol Ther. 96(2-3):67–202. https://doi.org/10.1016/S0163-7258(02)00298-X
36. Dewick PM (2001) The shikimate pathway: aromatic amino acids and phenylpropanoids. In Medicinal Natural Products: a Biosynthetic Approach. 2:137–186.
37. Ekalu A, Habila JD (2020) Flavonoids: isolation, characterization, and health benefits. Beni-Suef University J Basic Appl Sci 9(1):1–14
38. Iwashina T (2013) Flavonoid properties of five families newly incorporated into the order Caryophyllales. Bull Natl Mus Nat Sci. 39:25–51
39. N.G.H. Ferrara, J et al (2003) LeCouter The biology of VEGF and its receptors, Nat. Med. 9 (6): 669–676.
40. Hyder SM, Stancel GM (1999) Regulation of angiogenic growth factors in the female reproductive tract by estrogens and progestins. Mol Endocrinol. 13(6):806–811. https://doi.org/10.1210/mend.13.6.0308
41. Folkman J et al (1995) Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med. 1(1):27–31. https://doi.org/10.1038/nm0195-27
42. Koch AE et al (1998) Review: angiogenesis: implications for rheumatoid arthritis. Arthritis Rheum 41(6):951–962. https://doi.org/10.1002/1529-0131(199806)41:6<951::AID-ART2>3.0.CO;2-D
43. Ferrara N, Alitalo K et al (1999) Clinical applications of angiogenic growth factors and their inhibitors. Nat Med. 5(12):1359–1364. https://doi.org/10.1038/70928
44. Ferrara N et al (2004) Vascular endothelial growth factor: basic science and clinical progress, Endocr. Rev. 25(4):581–611
45. Powell J et al (1999) Update on hemangiomas and vascular malformations. Curr Opin Pediatr. 11(5):457–463. https://doi.org/10.1097/00008480-199910000-00015
46. Hanahan D et al (1998) A flanking attack on cancer. Nat Med. 4(1):13–14. https://doi.org/10.1038/nm0198-013
47. Mocanu MM, Nagy P, Szollosi J et al (2015) Chemoprevention of breast cancer by dietary polyphenols. Molecules. 20(12):22578–22620. https://doi.org/10.3390/molecules201219864
48. Guthrie, A.R.; Chow, H.S.; Martinez, J.A et al (2017). Effects of resveratrol on drug- and carcinogen-metabolizing enzymes, implications for cancer prevention. Pharmacol. Res. Perspect. 5: e00294, 1, DOI: https://doi.org/10.1002/prp2.294.
49. Kello M, Kulikova L, Vaskova J, Nagyova A, Mojzis J et al (2017) Fruit peel polyphenolic extract-induced apoptosis in human breast cancer cells is associated with ROS production and modulation of p38MAPK/Erk1/2 and the Akt signaling pathway. Nutr. Cancer 69(6):920–931. https://doi.org/10.1080/01635581.2017.1339819
50. Pandey, M.K.; Gupta, S.C.; Nabavizadeh, A.; Aggarwal, B.B et al (2017) Regulation of cell signaling pathways by dietary agents for cancer prevention and treatment. Semin. Cancer Biol. 46: 158–181, DOI: https://doi.org/10.1016/j.semcancer.2017.07.002.
51. Dandawate PR, Subramaniam D, Jensen RA, Anant S et al (2016) Targeting cancer stem cells and signaling pathways by phytochemicals: novel approach for breast cancer therapy. Semin. Cancer Biol. 40–41:192–208
52. Curti V, Di Lorenzo A, Dacrema M, Xiao J, Nabavi SM, Daglia M et al (2017) In vitro polyphenol effects on apoptosis: an update of literature data. Semin. Cancer Biol. 46:119–131. https://doi.org/10.1016/j.semcancer.2017.08.005
53. Coccia A, Mosca L, Puca R, Mangino G, Rossi A, Lendaro E et al (2016) Extra-virgin olive oil phenols block cell cycle progression and modulate chemotherapeutic toxicity in bladder cancer cells. Oncol. Rep. 36(6):3095–3104. https://doi.org/10.3892/or.2016.5150
54. Zielinska-Przyjemska M, Kaczmarek M, Krajka-Kuzniak V, Luczak M, Baer-Dubowska W et al (2017) The effect of resveratrol, its naturally occurring derivatives and tannic acid on the induction of cell cycle arrest and apoptosis in rat C6 and human T98G glioma cell lines. Toxicol In Vitro 43: 69–75. https://doi.org/10.1016/j.tiv.2017.06.004
55. Cerezo, A.B.; Winterbone, M.S.; Moyle, C.W.; Needs, P.W.; Kroon, P.A(2015) Molecular structure-function relationship of dietary polyphenols for inhibiting VEGF-induced VEGFR-2 activity. Mol. Nutr. Food Res.59:2119–2131.
56. Sarkar J, Nandy SK, Chowdhury A, Chakraborti T, Chakraborti S (2016) Inhibition of MMP-9 by green tea catechins and prediction of their interaction by molecular docking analysis. Biomed. Pharmacother. 84:340–347. https://doi.org/10.1016/j.biopha.2016.09.049
57. Liu L, Lai CQ, Nie L, Ordovas J, Band M, Moser L, Meydani M et al (2008) The modulation of endothelial cell gene expression by green tea polyphenol-EGCG. Mol. Nutr. Food Res. 52(10):1182–1192. https://doi.org/10.1002/mnfr.200700499
58. Gomes F.G., Nedel F., Alves A.M., Nor J.E., Tarquinio S.B et al (2013) Tumor angiogenesis and lymphangiogenesis: tumor/endothelial crosstalk and cellular/microenvironmental signaling mechanisms. Life Sci. 92: 101–107, 2, DOI: https://doi.org/10.1016/j.lfs.2012.10.008.
59. Verheul H.M., Pinedo H.M et al (2000) The role of vascular endothelial growth factor (VEGF) in tumor angiogenesis and early clinical development of VEGF-receptor kinase inhibitors. Clin. Breast Cancer. 1(Suppl. S1): S80–S84
60. McMahon G et al (2000) VEGF receptor signaling in tumor angiogenesis. Oncologist. 5(Suppl. S1): 3–10
61. Ferrara N, Gerber HP, LeCouter J et al (2003) The biology of VEGF and its receptors. Nat. Med. 9(6):669–676. https://doi.org/10.1038/nm0603-669
62. Lieu C, Heymach J, Overman M, Tran H, Kopetz S et al (2011) Beyond VEGF: inhibition of the fibroblast growth factor pathway and antiangiogenesis. Clin. Cancer Res. 17(19):6130–6139. https://doi.org/10.1158/1078-0432.CCR-11-0659
63. Carmeliet P., Jain R.K et al (2011) Molecular mechanisms and clinical applications of angiogenesis. Nature. 473: 298–307, 7347, DOI: https://doi.org/10.1038/nature10144
64. Bergers G, Hanahan D et al (2008) Modes of resistance to anti-angiogenic therapy. Nat. Rev. Cancer. 8(8):592–603. https://doi.org/10.1038/nrc2442
65. Giacomini A, Chiodelli P, Matarazzo S, Rusnati M, Presta M, Ronca R et al (2016) Blocking the FGF/FGFR system as a "two-compartment" antiangiogenic/antitumor approach in cancer therapy. Pharmacol. Res 107: 172–185
66. Brahimi-Horn MC, Pouyssegur J et al (2005) The hypoxia-inducible factor and tumor progression along the angiogenic pathway. Int. Rev. Cytol. 242: 157–213. https://doi.org/10.1016/S0074-7696(04)42004-X

67. Yang Y, Sun M, Wang L, Jiao B et al (2013) HIFs, angiogenesis, and cancer. J. Cell. Biochem. 2013(114):967–974
68. Hickey M.M., Simon M.C et al (2006) Regulation of angiogenesis by hypoxia and hypoxia-inducible factors. Curr. Top. Dev. Biol. 76: 217–257, DOI: https://doi.org/10.1016/S0070-2153(06)76007-0.
69. Genis L., Galvez B.G., Gonzalo P., Arroyo A.G et al (2006) MT1-MMP: uUniversal or particular player in angiogenesis? Cancer Metastasis Rev. 25: 77–86, 1, DOI: https://doi.org/10.1007/s10555-006-7891-z.
70. Hung H et al (2014) Inhibition of estrogen receptor alpha expression and function in MCF-7 cells by kaempferol. J Cell Physiol. 198:197–208
71. Luo H, Rankin GO, Liu L, Daddysman MK, Jiang BH, Chen YC et al (2009) Kaempferol inhibits angiogenesis and VEGF expression through both HIF dependent and independent pathways in human ovarian cancer cells. Nutr Cancer. 61(4):554–563. https://doi.org/10.1080/01635580802666281
72. Liu X, Tian S, Liu M, Jian L, Zhao L et al (2016) Wogonin inhibits the proliferation and invasion, and induces the apoptosis of HepG2 and Bel7402 HCC cells through NFkappaB/Bcl-2, EGFR and EGFR downstream ERK/AKT signaling. Int. J. Mol. Med. 4:1250–1256
73. Chen XM, Bai Y, Zhong YJ, Xie XL, Long HW, Yang YY, Wu SG, Jia Q, Wang XH et al (2013) Wogonin has multiple anti-cancer effects by regulating c-Myc/SKP2/Fbw7alpha and HDAC1/HDAC2 pathways and inducing apoptosis in human lung adenocarcinoma cell line A549. PLoS ONE 11: e79201
74. Dai Z.J., Wang B.F., Lu W.F., Wang Z.D., Ma X.B., Min W.L., Kang H.F., Wang X. J., Wu W.Y et al (2013). Total flavonoids of Scutellaria barbata inhibit invasion of hepatocarcinoma via MMP/TIMP in vitro. Molecules. 1: 934–950.
75. Lin C-W, Chen P-N, Chen M-K, Yang W-E, Tang C-H, Yang S-F, Hsieh YS (2013) Kaempferol reduces matrix metalloproteinase-2 expression by down-regulating ERK1/2 and the activator protein-1 signaling pathways in oral cancer cells. PLoS ONE 8(11):e80883. https://doi.org/10.1371/journal.pone.0080883

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