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 NFκB, 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
| 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; Induce 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-1a ↓; 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/smads signaling pathways ↓; VEGF ↓; ERK1/2/MAPK, AKT/P38K/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           | Scutellaria bisexualis | HePG2             | MMP-9 ↓ | Hong et al. [16] |
| 9     | Hesperadin        | Citrus fruits | Mice              | MMP-9 ↓; mitogen MAPK ↓ | Lee et al. [17] |
| 10    | Oroxyloside       | Scutellaria bisexualis | EA.hy926 cells | Akt/MAPK/NF-kB 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/P38K/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, flavanones, 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 supplemen 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]](image-url)
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 tyrosine 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 cellular 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 VEGFR2 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
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
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].
Quercetin is a flavonoid which is abundantly found in vegetables and fruits. Lupo et al. [21] studied the antian‐
giogenic 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.

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

**Fig. 6** A representation describing the molecular mechanism of delphinidin on the antiangiogenic activity in A 549 cells
Abbreviations
VEGF: Vascular endothelial growth factor; VEGFRI: Vascular endothelial growth factor receptor; BFGR: 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 tyrosine 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; PK3K: 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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All the authors declare that they have no competing interests.

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References
1. Chen L, Yang B, Tang B, Gong G, Kim 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: involvement of ERK/VEGF/KDR signaling pathway. Fitoterapia. 111:78–86. https://doi.org/10.1016/j.fitotec.2014.04.015
3. Hu WH, Wang HY, Xia YT, Dai DK, Xiong QP, Dong TX, Duan R, Chan QKL, Qin QW, Tsai KKW (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(2):219–227. https://doi.org/10.15438/jcp.2017.22.4219
8. Santosh W et al (2014) Anti-angiogenic activity of natural flavonoid myricitin on chick chorioallantoic membrane (cham) in-vivo. Int J Pharmacy. 416:0–165
9. Zhang M, Lu L, Zhang B, Zhu Z, Li J, Zhu Z, Yan M, Liu B (2017) Luteolin suppresses angiogenesis and vasogenic mimicry formation through inhibiting Notch1-VEGF signaling in gastric cancer. Biochemical and Biophysical research communications. 490(5):913–919. https://doi.org/10.1016/j.bbrc.2017.06.140
10. Pervin M, Unno K, Nakamura Y, Imi S et al (2016) Luteolin suppresses ultraviolet A- and B-induced matrix metalloproteinases-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.11-7890
12. Liao ZH, Zhu HQ, Chen YY, Chen RL, Fu LX, Li L, Zhu H, Zhou JL, Liang G (2020) The epigallocatechin gallate derivative Y6 inhibits human hepaticoportal carcinoma by inhibiting angiogenic 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/Smad signaling in human umbilical vein endothelium cells. Biomed Pharmacotherapy. 120:109491. https://doi.org/10.1016/j.biopha.2019.109491
14. Chen SI, 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 Ther 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) Nobleinin suppresses MMP-9 expression through modulation of p38 MAPK activity in human dermal fibroblasts. Biol Pharm Bull. 37(11):158–163. https://doi.org/10.1248/bbpb.13-05534
16. Hong M, Cheng H, Song J, 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 AR, Kim SM, 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, Dong Y, Zhu Y, Li Z, … Luo N et al (2017) Oroxylside 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. Lui L, Fan P, Zhou 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.bioch.2019.05.003
20. Kim M-H, Jeong Y-J, Cho H-J, Hye 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. Lupu G, Cambria MT, Oliveri M, Rocco C, Capporalelo N, Longo A, Zanghi G, Salmeri M, Fost 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
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., Gonzalez P., Arroyo A.G et al (2006) MT1-MMP: Universal or particular player in angiogenesis? Cancer Metastasis Rev. 25: 77–86, 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/SK2/Fbw7alpha and HDAC1/HDAC2 pathways and inducing apoptosis in human lung adenocarcinoma cell line A549. PLoS ONE 11: e79201
74. Dai ZJ, Wang BF, Lu WF, Wang ZD, Ma XB, Min WL, Kang HF, Wang XJ, Wu WY 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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