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REVIEW ARTICLE

Anti-Angiogenic Activity of Curcumin in Cancer Therapy: A Narrative Review

Abolfazl Shakeri[1], Natalie Ward[2], Yunes Panahi[3] and Amirhossein Sahebkar[4,5,6,*]

[1]*Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran;* [2]*School of Biomedical Sciences & Curtin Health Innovation Research Institute, Curtin University, Perth Australia;* [3]*Pharmacotherapy Department, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran;* [4]*Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran;* [5]*Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran;* [6]*School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

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Abstract: Curcumin is a naturally occurring polyphenol isolated from *Curcuma longa* that has various pharmacological activities, including, anti-inflammatory, anti-oxidant and anti-cancer properties. The anticancer effect of curcumin is attributed to activation of apoptotic pathways in cancer cells, as well as inhibition of inflammation and angiogenesis in the tumour microenvironment and suppression of tumour metastasis. Angiogenesis, which is the formation of new blood vessels from pre-existing ones, is a fundamental step in tumour growth and expansion. Several reports have demonstrated that curcumin inhibits angiogenesis in a wide variety of tumour cells through the modulation of various cell signaling pathways which involve transcription factors, protein kinases, growth factors and enzymes. This review provides an updated summary of the various pathways and molecular targets that are regulated by curcumin to elicit its anti-angiogenic activity.

Keywords: Curcuminoids, neovascularization, cancer, vascular endothelial growth factor, angiogenesis, obesity.

1. INTRODUCTION

Angiogenesis, the formation of new blood vessels from pre-existing ones *via* sprouting, is fundamental for several physiological and pathological processes, including embryonic development, wound healing and uterus function [1]. However, angiogenesis can also aggravate tumour progression, some retinal diseases and obesity [2]. There are approximately 30 activators of angiogenesis and a similar number of inhibitors [3].

Recently, many potential anti-angiogenic targets have been discovered including vascular endothelial growth factor (VEGF), hypoxia inducible factor-1α (HIF-1α), basic fibroblast growth factor (bFGF), matrix metalloproteinase (MMPs), platelet-derived growth factor (PDGF), angiopoietins (ANG-1 and ANG -2) and interleukin 8 (IL-8), IL-2 and IL-17 [4, 5]. Of them, VEGFs and their receptors (VEGFR1, VEGFR2, and VEGFR3), which are characterized by tyrosine kinase activity, play essential roles in angiogenesis [4]. Some anti-VEGF agents including bevacizumab, pegaptanib and ranibizumab are currently used in the treatment of retinal and ocular diseases, multiple solid and haematological malignancies, and some multi-targeted VEGFR tyrosine kinase inhibitors (TKI) including sunitinib, sorafenib, pazopanib, vandetanib, vatalanib, cabozantinib, axitinib, and regorafenib that have been approved by the US FDA [6-9]. However, several of these drugs have been found to have side effects, such as malignant hypertension as well as cardiovascular, cutaneous, renal, hepatic and haematological toxicities [7]. Therefore, there is a need for safe anti-angiogenic drugs.

Recently, several bioactive compounds with anticancer effects have been of interest. Some studies have demonstrated that plant-derived natural products are able to reduce or inhibit angiogenesis [10], with the naturally occurring polyphenols receiving considerable attention. Curcumin (Fig. **1A**), a naturally occurring polyphenol isolated from *Curcuma longa*, has numerous activities including anti-inflammatory, antioxidant, neuroprotective and anti-angiogenic properties [11-22]. Several studies have indicated that curcumin is quite safe even at doses as high as 12 g/day [23]. Curcumin has anti-tumour properties [23-27] and can inhibit various cell signaling proteins involved in angiogenesis, cell proliferation, metastasis, radioresistance and chemoresistance [28]. These can include activator protein 1 (AP-1), nuclear factor-kappa B (NF-κB), interleukins (IL-6), cyclooxygenase-2 (COX-2), reactive oxygen species (ROS),

*Address correspondence to this author at the Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, P.O. Box: 91779-48564, Iran;
Tel: 985118002288; Fax: 985118002287;
E-mails: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

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MMPs, cyclin D1, epidermal growth factor receptor (EGFR), Akt, β-catenin, as well as tumour necrosis factor (TNF). However, the anti-angiogenesis potential of curcumin has not been fully understood and studied.

The present review summarizes recent research (2009-2017) on the angiogenesis activity of curcumin. Since Previous reviews on this important and rapidly expanding topic date back to 2008 and before [29], we aimed to focus on the recent findings in this field and provide an updated view as to the anti-angiogenic properties of curcumin with a particular emphasis on cancer.

2. SEARCH

The search strategy in this study involved the use of relevant key words such as (curcumin OR curcuminoids OR "*Curcuma longa*") in combination with (angiogenesis OR angiogenic OR anti-angiogenic OR VEGF OR "vascular endothelial growth factor"). Search was performed Web of Science, PubMed, Scopus, ScienceDirect and Google Scholar databases. All papers published in English language assessing the effect of curcumin on angiogenesis, regardless of the type of disease, were included.

3. TARGETS OF CURCUMIN IN TUMOUR ANGIOGENESIS

3.1. Human Glioblastoma Cells

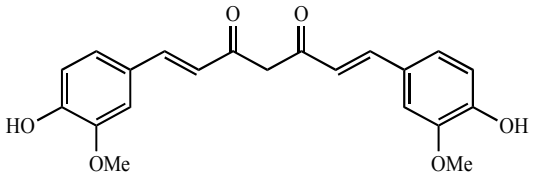
Curcumin suppressed growth of U-87 human glioblastoma cells in xenograft models in athymic mice [30]. *In vitro* experiments revealed that the anti-angiogenic activity of curcumin was partly due to the inhibition of endothelial cell migration across the extracellular matrix and morphogenic differentiation of RBE4 brain endothelial cells into capillary-like structures [30]. Curcumin also decreased the gelatinolytic activities of MMP9 in gliomas *in vivo* [30]. Therefore, the mechanisms of the anti-tumour effects of curcumin may be related to the inhibition of glioma-induced angiogenesis [30]. This data is in agreement with a previous study where curcumin inhibited the enzymatic activity of MMP-9 in U-87 cells [31].

3.2. Breast Cancer Cells

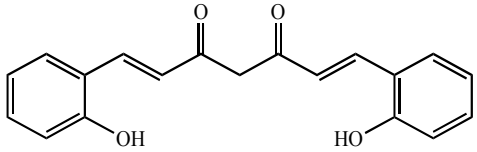
In vitro experiments demonstrated that curcumin inhibited proliferation and enhanced apoptosis of MDA. MB231 breast cancer cells [32]. *In vivo* data also showed that curcumin inhibited tumour growth and angiogenesis by influencing the expression of NF-κB-regulated gene products (cyclin D1, PECAM-1 and p65) [32].

3.3. Pancreatic Cancer Cells

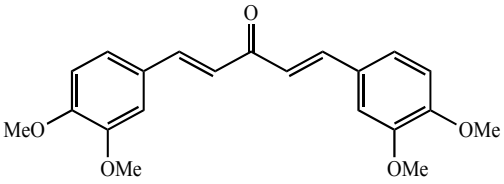
Curcumin was also able to inhibit the proliferation and enhance apoptosis of MIA PaCa-2 human pancreatic cancer cells [33]. *In vivo* experiments showed that curcumin inhibited tumour growth and angiogenesis in an orthotopic model of pancreatic cancer through the expression of several important proteins regulated by NF-κB as well as down regulation of the NF-κB-regulated gene products (cyclin D, VEGF, MMP-9 and IKKα/β [33]). Curcumin significantly inhibited endothelial progenitor cell proliferation, which was accompanied by a significant increase in the expression of p21 and a slight increase in p53, indicative of inhibited cell proliferation during the G1 to S phase transition of the cell cycle [34]. There was also a significant decrease in the



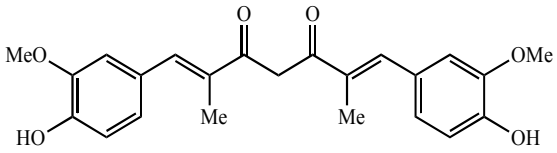
A. Curcumin (Cur)



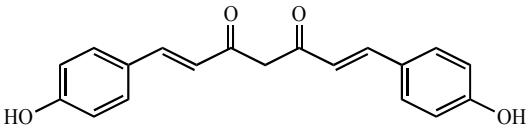
B. bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione (BDMC-A)



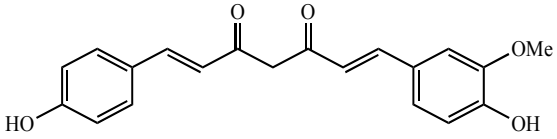
C. (1E, 4E)-1, 5-bis (2-methoxyphenyl) penta-1, 4-dien-3-one (B19)



D. 1,7-bis(4-hydroxy-3-methoxyphenyl)2,6 dimethyl-hepta-1,6-diene-3,5-dione



E. Bisdemethoxycurcumin (BDMC)



F. Demethoxycurcumin

Fig. (1). The chemical structure of curcumin derivatives. (**A**) Curcumin. (**B**) BDMC-A. (**C**) B19. (**D**) 1,7-bis(4-hydroxy-3-methoxyphenyl)2,6 dimethyl-hepta-1,6-diene-3,5-dione. (**E**) BDMC. (**F**) DC. BDMC: bisdemethoxycurcumin; DC: demethoxycurcumin.

formation of endothelial progenitor cell colonies in the presence of curcumin [34].

3.4. Targets of Curcumin in Non-Cancerous Diseases

Zhang *et al*. [35] have investigated the inhibitory effect of curcumin on endometriosis (EMS) and its influence on VEGF and microvessel density in eutopic and ectopic endometrium of experimental rats. The rat model of endometriosis, eutopic and ectopic endometrium exhibited different responses to curcumin in regards to angiogenesis. Curcumin inhibited ectopic endometrium angiogenesis through inhibition of the secretion of pro-angiogenic factors thereby mitigating or preventing the occurrence and development of EMS [35]. Curcumin was found to decrease the quantity of microvessels and VEGF protein expression in the heterotopic endometrium of EMS rats [35].

Curcumin attenuated sinusoidal angiogenesis in liver fibrosis possibly by targeting hepatic stellate cells (HSCs) via a PPAR-c activation-dependent mechanism [36]. It also suppressed multiple pro-angiogenic factors including vWF, CD31, VEGFR-1, VEGFR-2, placental growth factor and cyclooxygenase-2 in rat fibrotic liver [36]. In another study, curcumin similarly suppressed multiple pro-angiogenic factors in rat fibrotic liver [37].

Curcumin inhibited adipokine-induced angiogenesis of human umbilical vein endothelial cells [38]. Supplementing the high-fat diet of mice with curcumin reduced body weight gain, adiposity, and microvessel density in adipose tissue, which coincided with reduced expression of VEGF and its receptor VEGFR-2 [38]. Curcumin blocked indomethacin-induced gastric ulceration by induction of collagenization and angiogenesis in gastric tissues via upregulation of MMP-2, membrane type (MT) 1-MMP, VEGF, and transforming growth factor (TGF)-β at protein and messenger ribonucleic acid (mRNA) levels [39]. Kant *et al*. [40] have reported that curcumin heals indomethacin-induced gastric ulceration by stimulation of angiogenesis *via* upregulation of VEGF and TGF-β1 and accelerated healing in dexamethasone impaired wounds via enhanced expression of TGF-β1 and its receptors. Curcumin enhanced the neovascularization at diabetic wound sites directly, by the increased expression of angiogenic factors such as VEGF, TGF-β1, and other factors such as HIF-1α, SDF-1α, and HO-1, as well as indirectly, by anti-inflammatory and antioxidant action [40] (Fig. **2**).

4. EFFECT OF CURCUMIN ON MIGRATION, INVASION AND METASTASIS

Since tumour growth and metastasis are dependent on the formation of new blood vessels, targeting angiogenesis is a promising treatment target for cancer. Most cancer death is caused by the invasive spread to secondary sites (metastasis) [41]. Since curcumin can inhibit transcription factors such as NF-κB and AP-1, it can reduce invasion of cells *in vitro* and *in vivo* by regulation of invasive genes such as extracellular matrix (ECM) degradation enzymes (MMP-9, MT1-MMP, and MMP-2) [42]. Many *in vitro* and *in vivo* studies have demonstrated that curcumin is able to suppress invasion and metastasis of a variety of cancer cells [43].

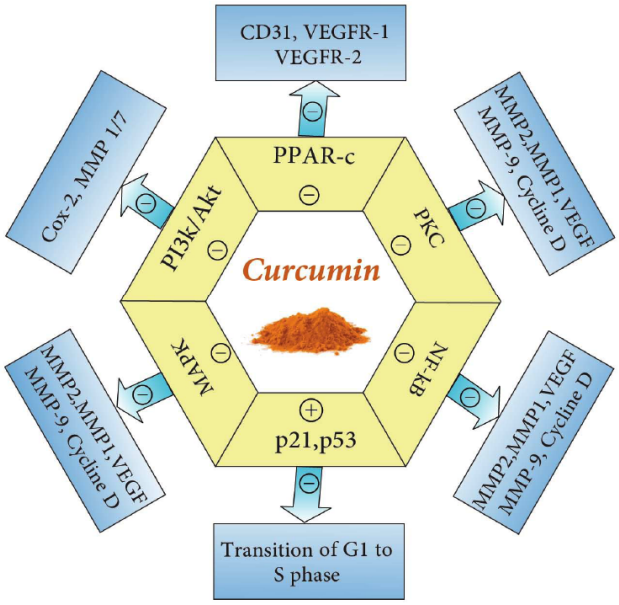


Fig. (2). Molecular targets underlying anti-angiogenic effects of curcumin in tumour. PPAR: peroxisome proliferator-activated receptor; VEGF: vascular endothelial growth factor; Cox: cyclooxygenase; PKC: protein kinase C; MMP: matrix metalloproteinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphoinositide 3-kinase.

4.1. Thyroid Cancer Cell Lines

The effects of curcumin on migration and invasion of human thyroid cancer cell lines FTC133 were investigated. Curcumin inhibited the adhesion, migration, and invasion of FTC133 cell lines *in vitro* and suppressed the expression and activation of MMP-1/7 and COX-2 by inactivation of the PI3K/Akt signaling pathway [44]. In another study, curcumin inhibited the invasion and metastasis of papillary thyroid cancer cells by suppressing the TGF-β/Smad2/3 pathway and subsequently down- regulating the expression of MMP-2 and MMP-9 matrix metallo-proteinases. These results demonstrated that curcumin inhibited the TGF-β1-induced epithelial-mesenchymal transition (EMT) *via* down-regulation of Smad 2/3 signaling pathways [45]. Curcumin also inhibited K1 papillary thyroid cancer cell attachment, spread, migration and invasion, as well as the expression and activity of MMP-9 [46].

4.2. Hepatocellular Carcinoma Cell

Curcumin suppressed phthalate-induced cell migration, invasion and epithelial-mesenchymal transition, decreased the proportion of cancer stem cell (CSC)-like cells in hepatocellular carcinoma cell lines *in vitro*, and inhibited tumour growth and metastasis *in vivo* through inhibition of the aryl hydrocarbon receptor/ERK/SK1/ sphingosine 1-phosphate receptor signaling pathways [47].

4.3. Prostate Cancer Cells

Curcumin has been shown to interrupt an important positive feedback loop between the cytokines CXCL1/-2 and NFκB in prostate cancer (PC3 cells) that is responsible for the activation of several mediators of metastasis [48]. In-

deed, *in vivo* experiment demonstrated that curcumin treated animals show a significant reduction in the number of lung metastases formed from circulating PC3 cells [48].

4.4. Colorectal Cancer Cells

Furthermore, curcumin suppressed cell proliferation, tumour growth, invasion and *in vivo* metastasis, and stabilized the expression of the tumour suppressor Pdcd4 in colorectal cancer (CRC) [49]. Chen *et al*. [49] have shown that curcumin significantly inhibited CRC cell migration and invasion *in vitro* through suppression of focal adhesion kinase (FAK) activation. Curcumin was also shown to enhance cell adhesion ability by increasing ECM components and promotion of E-cadherin expression in CRC cells, while reducing tumour growth and liver metastasis *in vivo via* downregulation of Sp-1 transcription factor and its downstream signals [50].

4.5. Lung Cancer Cells

Chen *et al*. [50] studied the *in vitro* and *in vivo* effects of curcumin on the migration and invasion of human lung cancer cells. The reduction in metastasis observed in curcumin-treated cells was attributed to the inhibition of Rac1/PAK1 pathway signaling and decreased MMP-2 and MMP-9 expression [51]. This data is in agreement with a previous study where curcumin inhibited the migration and invasion of lung cancer by modulating GLUT1/MT1-MMP/MMP2 pathway [36]. In another study, curcumin inhibited the migration and invasion of human A549 lung cancer cells *in vitro* through the MEKK3, p-ERK signaling pathways, resulting in inhibition of MMP-2 and MMP-9 [51].

4.6. Breast Cancer Cells

Curcumin inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced MMP-9 expression and invasion in MCF-7 cells through suppressing of the PKC, MAPK and NF-κB/AP-1 pathway [42].

5. EFFECTS OF CURCUMIN FORMULATIONS AND DERIVATIVES ON ANGIOGENESIS

A number of limitations exist over the use of curcumin, including instability at physiological pH, low solubility in water and low bioavailability [52]. Several drug delivery strategies, including the use of nano-carriers, have been developed to improve this. Gong *et al*. [53] have investigated the anti-angiogenesis and anti-tumour activity of curcumin loaded polymeric micelles (curcumin micelles) *in vitro* and *in vivo*. The micelles were shown to have a stronger inhibitory effect on proliferation, migration, invasion, and tube formation of HUVECs than free curcumin. Compared with free curcumin, curcumin micelles were more effective in suppressing tumour growth and metastasis and prolonged survival in LL/2 mouse models [53]. Similar results were reported by Gao *et al*. [54]; monomethoxy poly (ethylene glycol) poly (lactide) copolymer (MPEG-PLA) micelles (curcumin/MPEG-PLA) showed improved anti-angiogenesis and anti-tumour activity *in vitro* and *in vivo* compared with free curcumin. This suggests that curcumin/MPEG-PLA could improve the anti-lung metastasis effect of curcumin *in vivo* [54]. Curcumin formulated with phosphatidylcholine (Meriva) significantly reduced the expression of MMP-9 and lung metastasis of a mammary gland tumour cell line [55]. Both free curcumin and Meriva had no significant effect on the tumour volume *in vivo*. In contrast, Meriva significantly inhibited the metastasis of the cells to the lung while free curcumin had no significant effect [55]. The inhibitory effects of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione (BDMC-A) (Fig. **1B**), an analogue of curcumin, on invasion, angiogenesis and metastasis markers using MCF-7 cells and *in silico* studies, have also been investigated [56]. BDMC-A more effectively inhibited invasion, angiogenesis and metastasis markers compared with curcumin [56]. This was attributed to the presence of a hydroxyl group in the ortho position of its structure. Mechanistic studies revealed that BDMC-A might exert its activity by inhibiting metastatic and angiogenic pathways *via* modulation of the expression of proteins upstream of the NF-kB (TGF-b, TNF-a, IL-1b and c-Src), and NF-kB signaling cascade (c-Rel, COX-2, MMP-9, VEGF, IL-8), and by upregulating TIMP-2 levels [56]. Anti-angiogenic activity of (1E, 4E)-1, 5-bis (2-methoxyphenyl) penta-1, 4-dien-3-one, a mono-carbonyl analogue of curcumin (B19) (Fig. **1C**), with higher bioavailability, was investigated both *in vitro* and *ex vivo*. The anti-angiogenic activity of B19 was better than curcumin [57]. It inhibited migration and tube formation in human umbilical vein endothelial cells, arrested microvessel outgrowth from rat aortic rings, and suppressed the neovascularization of chicken chorioallantoic membrane [57]. Mechanistic studies revealed that B19 suppressed the downstream protein kinase activation of VEGF by decreasing phosphorylated forms of serine/threonine kinase Akt, extracellular signal-regulated kinase, and p38 mitogen-activated protein kinase [57]. The anti-angiogenic ability of 1,7-bis(4-hydroxy-3-methoxyphenyl)2,6 dimethyl-hepta-1,6-diene-3,5-dione, a curcumin derivative (Fig. **1D**), which is substituted with a methyl group at both C2 and C6 positions has also been investigated. The *in vitro* anti-angiogenesis activity of this compound was significantly greater than that of curcumin against endothelial cell migration, invasion, and tube formation and was demonstrated to be due to the suppression of VEGFR2-mediated ERK1/2 signaling pathway [58].

Bisdemethoxycurcumin (BDMC) (Fig. **1E**), one of the main derivatives of curcumin present in turmeric, significantly inhibited the adhesion, migration, invasion and metastasis of the human ovarian cancer cell line SKOV-3 [59]. Moreover, BDMC inhibited expression of several degradation-associated proteins, such as MMP-2, MMP-9, CD147, urokinase plasminogen activator (uPA), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), while increasing the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1), in a dose dependent manner [59]. BDMC also inhibited the invasion and metastasis of SKOV-3 cells by influencing the degradation of extracellular matrix and basement membrane factors [59]. Xu *et al*. [60] have reported that BDMC inhibited highly metastatic large-cell lung cancer 95D cell migration and invasion through the inhibition of vimentin and the promotion of E-cadherin expression [60]. Demethoxycurcumin (DC) (Fig. **1F**), another active analogue of curcumin in turmeric, inhibited capillary formation of rat aortic rings and the

neovascularization of CAM without showing any toxicity. DC inhibited angiogenesis through suppression of MMP-9 expression [61]. Huang *et al*. [62] investigated the *in vitro* anti-angiogenesis effect of three main curcumin derivatives (curcumin, DC and BDMC). The proliferative effect of curcumin on HUVECs was greater than that observed for the other two derivatives. However, all three curcumin derivatives could prevent angiogenesis by inhibiting proliferation and migration of endothelial cells and down-regulating the expression of VEGF and adhesion molecules ICAM-1 [62].

6. EFFECT OF CURCUMIN ON miRNA REGULATION INVOLVED IN ANGIOGENESIS

microRNAs (miRNAs) are small non-coding RNA molecules with about 20-22 nucleotides, which can be widely involved in the biological processes of proliferation, apoptosis and differentiation of cells and play a key role in the regulation of onset and development of many diseases such as cardiovascular diseases and tumours [63, 64]. miRNAs have been identified as a type of angiogenic regulators by down-regulating the expression of pro-angiogenic or antiangiogenic factors [65]. So far, a number of angiogenesis-regulatory miRNAs have been identified; miR-126, miR-27b, Let-7b,f, miR-93, miR-210, miR-378a, miR-296, miR-10b, miR-196b, miR-130a, miR-132, miR-497/VEGF-A are known as proangiogenic while miR-20a/ miR-20b, miR-519c, miR-214, miR-200 family, miR-107, miR-15a, miR-16, miR-199a, miR-125b, miR-361-5p, miR-1/206, miR-503, miR-128, miR-145, miR-26a, miR-34 family, miR-26b-5p, miR-218, miR-137, miR-195a-3p, miR-17-92 and miR-124 are known to have anti-angiogenic activity [66, 67]. Recently, miRNA regulation by curcumin in cancer therapy has been received more attention. Curcumin has been found to modulate the expression of several miRNAs in different human cancer cells [68]. Zhou *et al*. [69] reported that there are several miRNAs including miR-21, miR-22, miR-34a, miR-125a-5p, miR-181b, miR-221, miR-200b/c and miR-874 that have crucial roles in the process of tumour cell invasion and metastasis by targeting downstream genes such as Erbb3, P53, Bcl-2, p27kip1, AP-1, PDCD4, MMPs, and HMGA2 [69]. Curcumin inhibited the transcriptional regulation of miR-21 and down-regulated miR-21 expression *via* AP-1 which suppressed the invasion and *in vivo* metastasis in CRC [48]. Curcumin also inhibited migration and invasion *in vitro via* up-regulation of miR-7 and subsequent down-regulation of SET8 and its downstream effects, including p53, in pancreatic cancer cells, as well as inhibited tumour growth and *in vivo* metastasis in CRC cells [70]. Curcumin also inhibited the expression of MMP-1 and -3 through upregulation of miR-181b in MDA-MB-231 breast cancer cells by binding to metastases related-cytokines (CXCL1 and CXCL2), leading to reduced invasion *in vitro* and *in vivo* models [71]. miR-22 was upregulated by curcumin subsequently increasing expression of Erbb3 (erythroblastic leukemia viral oncogene homolog 3) and inhibited the human Y79 red blood cells proliferation and reduced the migration [72]. Curcumin upregulated miR-203 in bladder cancer by promoting DNA hypomethylation of the miR-203 promoter that leads to inhibition of cellular proliferation, migration and invasion [73]. Curcumin inhibited nasopharyngeal carcinoma metastasis by inhibiting the expression of miR-125a-5p and subsequently increasing expression of P53 [69]. Recently, Jiao *et al*. have suggested miR-34a-5p, miR-34c-5p and miR-302b-3p by regulating CCND1, WNT1 and MYC may be involved in the inhibitory role of curcumin in lung cancer metastasis [74]. It was reported that down-regulation of miR-221 by curcumin can inhibit cell proliferation and migration in pancreatic cancer through up-regulation of p27kip1 and PTEN [75]. Re-expression of miR-200b/c, which is known to inhibit the metastasis, by curcumin caused decrease in expression of MMPs and re-expression of PTEN in pancreatic cancer cells [76, 77] (Fig. **3**).

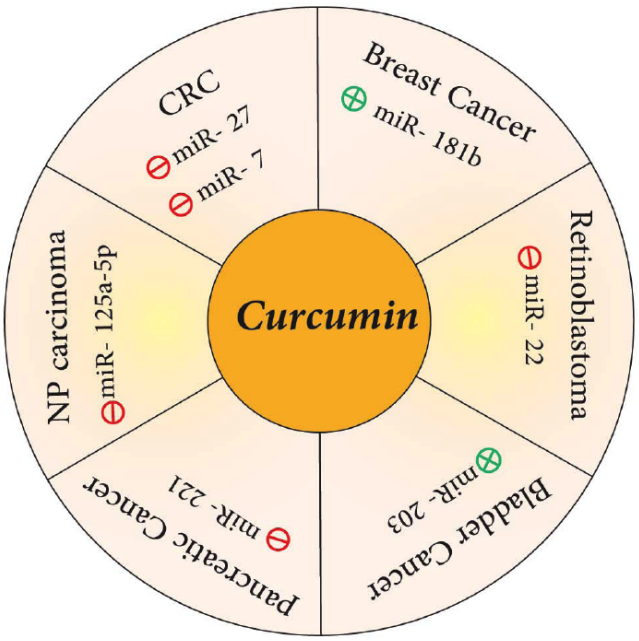


Fig. (3). Effect of curcumin on miRNAs involved in angiogenesis. NP: nasopharyngeal.

CONCLUSION

A number of *in vitro* and *in vivo* animal models have demonstrated the potential anti-angiogenic role of curcumin in cancer. These beneficial effects appear to be *via* inhibition of signalling pathways related to growth and proliferation and enhanced apoptotic signaling. Nevertheless limitations regarding the effective delivery and bioavailability of curcumin need to be addressed before curcumin can be used for its anti-angiogenic effect. Moreover, evidence from clinical studies with respect to the role of anti-angiogenic effect of curcumin in cancer and other studies is lacking. Hence, future studies are warranted to validate the efficacy of curcumin in angiogenesis-related diseases, in particular cancer.

LIST OF ABBREVIATIONS

AP-1	=	Activator Protein 1
ANG-1 and ANG-2	=	Angiopoietin 1 and 2
BDMC-A bFGF	=	Basic Fibroblast Growth Factor, bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione
BDMC	=	Bisdemethoxycurcumin
B19	=	(1E, 4E)-1, 5-bis (2-methoxyphenyl) penta-1, 4-dien-3-one

CSC	=	Cancer Stem Cell
COX-2	=	Cyclooxygenase-2
DC	=	Demethoxycurcumin
EGFR	=	Epidermal Growth Factor Receptor
EMS	=	Endometriosis
Erbb3	=	Erythroblastic Leukemia Viral Oncogene Homolog 3
ECM	=	Extracellular Matrix
HO-1	=	Heme Oxygenase-1
FAK	=	Focal Adhesion Kinase
GLUT1	=	Glucose Transporter 1
HMGA2HSCs	=	Hepatic Stellate Cells, High-Mobility Group AT-hook 2
HIF-1α	=	Hypoxia Inducible Factor-1α
ICAM-1	=	Intercellular Adhesion Molecule-1
IL-8	=	Interleukin 8
HIF-1α	=	Hypoxia-Inducible Factor 1-Alpha
MMPs	=	Matrix Metalloproteinase
MT1-MMP	=	Membrane Type 1 Metalloprotease
mRNA	=	Messenger Ribonucleic Acid
miRNAs	=	microRNAs
MAPK	=	Mitogen-Activated Protein Kinase
MPEG-PLA	=	Monomethoxy Poly (Ethylene Glycol) Poly (Lactide) Copolymer
NF-κB	=	Nuclear Factor-Kappa B
PPAR-c	=	Peroxisome Proliferator-Activated Receptors
PECAM-1	=	Platelet Endothelial Cell Adhesion Molecule
PDGF	=	Platelet-Derived Growth Factor
PAK1	=	p21-Activated Kinase 1
PKC	=	Protein Kinase C
Rac1	=	Ras-Related C3 Botulinum Toxin Substrate 1
ROS	=	Reactive Oxygen Species
SDF-1α	=	Stromal Cell-Derived Factor 1
TPA	=	12-O-Tetradecanoylphorbol-13-Acetate
TIMP-1	=	Tissue Inhibitor of Metalloproteinase-1
TGF	=	Transforming Growth Factor
TKI	=	Tyrosine Kinase Inhibitors
TNF	=	Tumour Necrosis Factor
uPA	=	Urokinase Plasminogen Activator
VEGF	=	Vascular Endothelial Growth Factor
VEGFR	=	Vascular Endothelial Growth Factor Receptor
vWF	=	von Willebrand Factor
VCAM-1	=	Vascular Cell Adhesion Molecule-1

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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