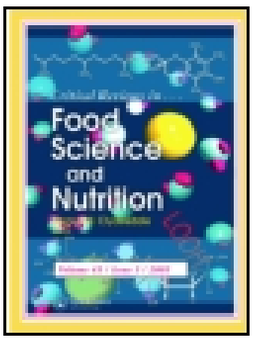

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Vascular endothelial growth factor: an important molecular target of curcumin

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Abbreviations

AMD Age-related macular degeneration

COX-2 cyclooxygenase-2

CRC colorectal cancer

EGFR epidermal growth factor receptor

hs-CRP high sensitive C-reactive protein

HUVEC human umbilical vein endothelial cell

HIMECs human intestinal microvascular endothelial cells

IBD inflammatory bowel disease

IL interleukin, iNOS: inducible nitric oxide synthase

MAPK Mitogen-activated protein kinase

mTOR the mammalian target of rapamycin

NFκB Nuclear factor kappa B

PDGF platelet derived growth factor

PlGF placental growth factor

RPE retinal pigment epithelium

ROS reactive oxygen species

TNF-α tumor necrosis factor- α

VEGF vascular endothelial growth factor

VEGFR VEGF receptor.

Abstract

The discovery of Vascular Endothelial Growth Factor (VEGF), the key modulator of angiogenesis, has triggered intensive research on anti-angiogenic therapeutic modalities. Although several clinical studies have validated anti-VEGF therapeutics, with few of them approved by the U.S. Food and Drug Administration (FDA), anti-angiogenic therapy is still in its infancy. Phytochemicals are compounds that have several metabolic and health benefits. Curcumin, the yellow pigment derived from turmeric (*Curcuma longa L.*) rhizomes, has a wide range of pharmaceutical properties. It has also been shown to inhibit VEGF by several studies. In this review, we elaborate the effect of curcumin on VEGF and angiogenesis and its therapeutic application.

Keywords

Curcumin; vascular endothelial growth factor; breast cancer; age-related macular degeneration; angiogenesis

Introduction

Angiogenesis is a process in which new blood vessels are formed from pre-existing vascular bed. The interactions between vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) with the mammalian target of rapamycin (mTOR) activate angiogenesis (Advani 2010). VEGF has a key role in both normal and pathological angiogenesis. The VEGF family consists of several members/subtypes including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF) (Shibuya 2011b). VEGF-A165 is the most important isoform for angiogenesis. Most of the biological properties of VEGF-A is exerted by its high affinity for the VEGF receptor (VEGFR)-1 and VEGFR-2 (Ferrara et al. 2003b). VEGF inhibitors are widely used for the treatment of several cancers such as ovarian, breast and colorectal cancer, and age-related macular degeneration (AMD) (Masoumi Moghaddam et al. 2012).

Phytochemicals are compounds that have several metabolic and health benefits. It has been shown that some anti-inflammatory phytochemicals can change the immunosuppressive tumor microenvironment (Chen et al. 2012b). Curcumin is a yellow pigment derived from turmeric (*Curcuma longa L.*) rhizomes with various pharmaceutical effects. Curcumin can be well tolerated and safe in long-term administration (Gupta et al. 2013). It can exert anti-inflammatory, antioxidant, anticancer and antimicrobial properties (Nagpal and Sood 2013). Curcuminoids have a significant effect on several inflammatory mediators including interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and high sensitivity C reactive protein (hs-CRP). It can also decrease serum concentrations of VEGF, IL-1β and IL-4, as shown in obese individuals (Ganjali et al. 2014a).

Inhibition of progestin-dependent secretion of VEGF is known as an effective strategy to control the spread of breast cancer (Carroll et al. 2013). Furthermore, VEGF is regarded as the most compelling angiogenic factor that its expression is regulated by nuclear factor (NF)-κB (Hoesel and Schmid 2013, Niu and Chen 2010). Curcumin may inhibit metastatic and angiogenic pathways in breast cancer cells by modulating the expression of proteins upstream to NF-κB and NF-κB signaling cascade including VEGF (Kunnumakkara et al. 2008). In vitro studies have reported that curcumin can reduce VEGF-A expression (Anand et al. 2011, Chakraborty et al. 2008, Farhangi et al. 2015). Curcumin can significantly reduce the expression of VEGFR2/3 and inhibit angiogenesis in a murine model of human breast cancer. Moreover, it can reduce reactive oxygen species (ROS) in AMD-retinal pigment epithelium (RPE) (Zhu et al. 2015) and the expression of platelet derived growth factor (PDGF) and VEGF genes (Ravindran et al. 2009). Curcumin was also shown to inhibit the expression and secretion of VEGF in a dose dependent manner (Fu et al. 2015b), but it has adverse effects on RPE cells at different concentrations (Woo et al. 2012).

It has been shown that VEGF and/or its receptor can be inhibited by several phytochemicals and natural products such as mastic oil, meisoindigo, artesunate, sulforaphane, aplidin, meisoindigo,4-O-methylgallic acid, celastrol, ellagic acid, delphinidin, curcumin and philinopside A, scopolin, fisetin and paeoniflorin, caffeic acid and Epigallocatechin gallate (EGCG) (Jeong, Koh, Lee, Lee, Lee, Bae, Lu and Kim 2011). In this review we will focus on the VEGF inhibitory effects of curcumin owing to the presence of extensive evidence on the anti-tumor properties of this phytochemical, which can be explained, at least in part, by the impact of curcumin on angiogenesis. Besides, curcumin has also been safely used in numerous clinical

trials that highlight the possibility of considering curcumin as a potential candidate for the treatment of human diseases in which angiogenesis is pathologically up-regulated.

VEGF and VEGFR

Angiogenesis is a process in which new blood vessels are formed from pre-existing vascular bed; VEGF plays a key role in both normal and pathological angiogenesis (Ferrara 2004). VEGF is most prominently involved in wound healing, the endometrial cycle and embryogenesis (Folkman and Shing 1992) but also in degenerative eye diseases (Bianchi et al. 2012), tumors (Folkman 1992), and inflammatory disorders such as joint disease (Brenchley 2000) and psoriasis (Narayanan et al. 2010). It has been reported that interaction between VEGF and PDGF with the mammalian target of rapamycin (mTOR) can activate angiogenesis. The mTOR has a key role in cell growth and proliferation (Tagawa et al. 2011). The family members of the VEGF and its receptor (VEGFR) play crucial roles in angiogenesis and lymphangiogenesis. In the 1990s, the genes of VEGF and VEGFR were characterized (Shibuya 2011a, Shibuya and Claesson-Welsh 2006). VEGF family members/subtypes involve VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF) (Kiselyov et al. 2007). VEGF-A may promote monocyte activation and chemotaxis (Clauss et al. 1990), regulate endothelial cell differentiation and increase vessel permeability (Ferrara et al. 2003a). It is the first factor known and has four isoforms including VEGF-A121, VEGF-A165, VEGF-A189 and VEGF-A206 (Shinkaruk et al. 2003). Of these, VEGF-A165 is the most important isoform for angiogenesis (Houck et al. 1992). PlGF and VEGF-B are involved in the cardiac muscle function, but they have a minor role in e angiogenesis regulation (Bry et al. 2010). VEGF-C and VEGF-D can regulate lymphangiogenesis (Alitalo and Carmeliet 2002). Furthermore, they may be involved in

angiogenesis at the early stage of embryogenesis and in tumor angiogenesis (Tammela et al. 2008). VEGFRs are cell membrane receptors which bind to VEGFs and can activate intracellular tyrosine kinases (Ferrara, Gerber and LeCouter 2003a). VEGFRs have an intracellular tyrosine kinase domain. There are three subtypes for VEGFRs including VEGFR-1, VEGFR-2, and VEGFR-3. The molecular organization is similar between the three receptors. The extracellular parts, composed of seven immunoglobulin (Ig)-like domains, bind the ligands to the Ig loops 2--3 that are involved to different extents in separate ligand-receptor combinations. In VEGFR-3, the amino terminal part of the extracellular domain is linked to the C-terminal part through a disulfide bond (Pajusola et al. 1994). The intracellular part contains two tyrosine kinase domains (TK1 and TK2). Tyrosine residues serving as autophosphorylation sites participate in signaling by binding Src homology 2 (SH2) (Roskoski 2005). The VEGFRs dimerize, get activated upon ligand-binding and initiate signal transduction pathways. Signaling is modulated through co-receptors such as heparan sulfate, neuropilins and integrins and by direct contacts between receptor molecules at Ig-loop7 that stabilizes the dimmer (Koch et al. 2011). The main effects of VEGFRs are: VEGFR-1 has an negative regulation of VEGFR-2 biology and determine the migration of monocytes; VEGFR-2 plays essential roles in vascular endothelial progenitors differentiation, vascular permeability, sprouting angiogenesis and endothelial migration, proliferation and survival; VEGFR-3 causes migration of lympho-endothelial precursors, lymphatic vessel expansion and blood vascular sprouting angiogenesis (Claesson-Welsh 2003). Most of the biological properties of VEGF-A is exerted by its high affinity for the VEGFR-1 and VEGFR-2 (Takahashi 2011). It has been shown that a soluble form of VEGFR-1 is associated with preeclampsia (Young et al. 2010), AMD (Luo et al. 2013) and nephrotic syndrome (Jin et

al. 2012). Function and structural features of the VEGF family members/subtypes and VEGFR are summarized in **Table 1**.

VEGF signal inhibitors, including anti-VEGF neutralizing antibodies and VEGFR kinase/multi kinase inhibitors, have been successfully developed and used for the treatment of cancer, being approved for a variety of solid tumors (Cohen et al. 2007, Hurwitz et al. 2004). VEGF inhibitors are also widely used for the treatment of several other disorders including psoriasis (Akman, Yilmaz, Mutlu and Ozdogan 2009, Narayanan, Callis-Duffin, Batten and Agarwal 2010, Xia et al. 2003) and ophthalmic diseases including premature retinopathy and AMD (Mintz-Hittner 2012, Shibuya 2014). Particularly in AMD, anti-VEGF signal inhibitors have been shown to be effective in suppressing disease symptoms. Intraocular injection of an anti-VEGF neutralizing antibody results in visual acuity improvement in AMD (Shibuya 2014).

Since VEGF signals play a key role in tumor angiogenesis, a number of antibodies and kinase inhibitors have been developed which can prevent VEGF-VEGFR signaling. These therapeutics are widely used for cancer treatment (Hurwitz, Fehrenbacher, Novotny, Cartwright, Hainsworth, Heim, Berlin, Baron, Griffing and Holmgren 2004). VEGF inhibitors such as the monoclonal antibody bevacizumab is approved as the first-line treatment for ovarian cancer (Han and Monk 2007). In preclinical studies and recent clinical trials, cediranib (AZD2171), an oral pan-VEGFR tyrosine kinase inhibitor, among several new molecules, was regarded as a promising agent with potent anti-angiogenesis properties (Decio et al. 2015b, Heckman et al. 2008, Ruscito et al. 2016). Decio et al. demonstrated that cediranib combined with platinum-based chemotherapy was able to reduce the spread of tumor and ascites development and was able to prolong overall survival of mice in a patient-derived ovarian cancer mouse xenograft model (Decio et al. 2015a).

Cediranib was also found to potentiate the chemotherapy effects, even in tumors that responded poorly to platinum agents (Decio, Cesca, Bizzaro, Porcu, Bettolini, Ubezio, Taraboletti, Belotti and Giavazzi 2015b, Heckman, Holopainen, Wirzenius, Keskitalo, Jeltsch, Ylä-Herttuala, Wedge, Jürgensmeier and Alitalo 2008, Ruscito, Gasparri, Marchetti, De Medici, Bracchi, Palaia, Imboden, Mueller, Papadia and Muzii 2016).

Curcumin

General characteristics

Phytochemicals are compounds that have several metabolic and health benefits (Visioli and Davalos 2011). It has been shown that some anti-inflammatory phytochemicals can change the immunosuppressive microenvironment prevalent in tumors by inhibiting NF-κB and proinflammatory cytokines (Chen, MIChAel and Butler-Manuel 2012a). Curcumin [diferuloylmethane; (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)] is a plant polyphenol with various pharmaceutical effects. Curcumin is a yellow pigment derived from turmeric (*Curcuma longa L.*) rhizomes (Epstein et al. 2010), which has a history of long-term safety (Dunbar et al. 2008). The majority of the effects of *Curcuma longa* are mainly attributed to curcumin, with potential effects against metabolic diseases (Mohammadi et al. 2013, Panahi, Hosseini, Khalili, Naimi, Soflaei, et al. 2016, Panahi, Khalili, et al. 2014, Rahmani et al. 2016, Sahebkar 2013, Sahebkar 2014b, Zabihi et al. 2016), cardiovascular diseases (Ganjali et al. 2017, Karimian, Pirro, Johnston, et al. 2017, Panahi, Ahmadi, et al. 2016, Panahi, Kianpour, et al. 2016, Sahebkar 2010), arthritis (Panahi, Rahimnia, et al. 2014a, Sahebkar and Henrotin 2016), pulmonary diseases (Lelli et al. 2017), cancer (Mirzaei et al. 2016, Momtazi and Sahebkar 2016, Momtazi, Shahabipour, et al. 2016, Teymouri et al. 2016), psychological diseases (Esmaily et al.

2015b, Panahi, Badeli, et al. 2015), dermatological disorders (Nguyen and Friedman 2013, Panahi, Sahebkar, Amiri, et al. 2012, Panahi, Sahebkar, Parvin, et al. 2012), and other chronic illnesses. Moreover, curcumin can improve several disorders such as sinusitis, rheumatisms, trauma, inflammatory skin ailments, allergies, ulcers, asthma, and diabetes (Goel et al. 2008), as well as anxiety (in obese individuals (Esmaily et al. 2015a)), quality of life and inflammation (in patients with solid tumors (Panahi, Saadat, et al. 2014).

Apart from curcumin (Abdollahi et al. 2017, Chrusciel et al. 2016, Ghandadi and Sahebkar 2016, Karimian, Pirro, Majeed, et al. 2017, Momtazi, Derosa, et al. 2016, Panahi, Alishiri, et al. 2016, Panahi, Ghanei, et al. 2015, Panahi, Hosseini, Khalili, Naimi, Simental-Mendia, et al. 2016, Panahi, Hosseini, Khalili, Naimi, Soflaei, Majeed and Sahebkar 2016, Panahi et al. 2017, Sahebkar 2014b, Sahebkar, Mohammadi, Atabati, Rahiman, Tavallaie, Iranshahi, Akhlaghi, Ferns and Ghayour-Mobarhan 2013, Sahebkar et al. 2017), there are others components in *Curcuma longa* called the curcuminoids group such as demethoxycurcumin and bis-demethoxycurcumin, which also have important pharmacological properties (Brondino et al. 2014, Chin et al. 2013, Manolova et al. 2014, Ramezani et al. 2017).

Curcumin bioavailability

Despite several beneficial pharmaceutical effects, curcumin has a low bioavailability (Anand et al. 2007). It has been shown that liposomes, nanoparticles and curcumin-phospholipid complex may improve its poor bioavailability (Mirzaei et al. 2017, Shoba et al. 1998). Moreover, some adjuvants such as piperine can reduce the conjugation of curcumin and its rapid removal from the urine (Bishnoi et al. 2011). There are several studies aiming to understand the bioavailability of curcumin. Yang et al. indicated that in rats, the oral bioavailability of curcumin was around

1% so very high doses of curcumin (3,600 to 12,000 mg) were necessary to achieve beneficial effects (Yang et al. 2007). When curcumin is administered to rats in a dose of 2000 mg/kg together with l-piperoyl piperidine that induces glucuronyl transferase enzymes, the bioavailability of curcumin increases around 154% (Shoba, Joy, Joseph, Majeed, Rajendran and Srinivas 1998).

High concentrations of curcumin metabolites as curcumin glucuronide and curcumin sulphate were detected in the plasma and urine of patients with advanced colorectal cancer refractory to standard chemotherapy after the oral consumption of curcumin capsules, suggesting that low bioavailability of curcumin is due to its rapid metabolism (Sharma et al. 2004). Pharmacokinetic and pharmacodynamic studies showed that during intestinal adsorption, curcumin undergoes a biotransformation to glucuronides of tetrahydrocurcumin and hexahydrocurcumin derivatives. In the liver, curcumin is initially transformed to dihydrocurcumin and tetrahydrocurcumin by reductases and later transformed into monoglucuronide conjugates as dihydrocurcumin-glucuronide and tetrahydrocurcumin-glucuronide by β-glucuronidase (Lin and Lin-Shiau 2001). In the gut and liver, the transformation can generate curcumin glucuronides and sulphates or reduced molecules like hexahydrocurcumin (Ireson et al. 2002, Pan et al. 1999, Pulido-Moran et al. 2016).

Antioxidant properties of curcumin

In vitro studies

Curcumin may exert anti-inflammatory, antioxidant, anticancer and antimicrobial effects (Maheshwari et al. 2006, Sahebkar, Mohammadi, Atabati, Rahiman, Tavallaie, Iranshahi, Akhlaghi, Ferns and Ghayour-Mobarhan 2013).

Several in vitro studies have reported the anti-oxidant property of curcumin. Cao et al, have shown that curcumin has an antioxidant activity in carcinogenesis (Cao et al. 2008). Dai, Tang, et al. have reported that curcumin can inhibit ROS formation and improve superoxide dismutase (SOD) activity and glutathione (GSH) level in human hepatocyte L02 cells (Dai, Tang, et al. 2015a).

Curcumin enhances the activity of heme oxygenase-1 (OH-1) in human endothelial cells. Jeong et al, have mentioned for the first time that the ortho-methoxy groups on the aromatic ring of curcuminoids are essential for increasing endothelial HO-1 expression (Jeong, Oh, Pae, Jeong, Kim, Shin, Seo, Han, Lee, Jeong, et al. 2006).

In vivo studies

Curcumin can protect against carcinogenesis by increasing antioxidant and phase II metabolizing enzymes such as glutathione S-transferase and quinone reductase in ddY male mice (Iqbal 2003). It can inhibit lipid peroxidation by scavenging hydroxyl and superoxide radicals in solid tumor-induced in mice (Ruby et al. 1995). In the liver from rats with hepatic injury and high levels of oxidative stress, a dose of 200 mg/kg of curcumin increased SOD and catalase activities as well as the hepatic total antioxidant capacity (Abdel-Daim and Abdou 2015).

In this context, there are some double clinical trials reported that curcumin can beneficially affect the pro-oxidant-antioxidant balance in obese individuals (Sahebkar, Mohammadi, Atabati, Rahiman, Tavallaie, Iranshahi, Akhlaghi, Ferns and Ghayour-Mobarhan 2013), and patients with arthritis (Panahi, Rahimnia, et al. 2014b).

Anti-inflammatory properties of curcumin

In vitro studies

Curcumin is capable to decrease inflammation with several mechanisms. Chronic diseases are caused by oxidative stress leading to chronic inflammation (Aggarwal 2010, Aggarwal and Harikumar 2009, Basnet and Skalko-Basnet 2011, Jurenka 2009, Recio et al. 2012, Reuter et al. 2010).

NF-κβ and TNF-α play a central role in the inflammatory response and their expression is modulated by ROS production (Sethi et al. 2008). Curcumin is an inhibitor of the mitogen-activated protein kinases (MAPKs) and NF-κB (Lee et al. 2005, Zhong et al. 2012), that regulate proinflammatory cytokine genes and chronic pain (Ji et al. 2009, Zhao et al. 2014). The inhibitory effect of curcumin on MAPKs and NF-κB has been reported in various cells such as MCF10A human breast epithelial cells (Lee et al. 2005), rat aortic smooth muscle cells (RASMCs) (Lee, Kim, Lee and Surh 2005, Zhong, Liu and Guo 2012), and the human synovial fibroblast cell line MH7A (Chandran and Goel 2012, Kloesch et al. 2013). Curcumin may downregulate oxidative stress and the subsequent inflammation through the Nrf2 pathway. Furthermore, in various types of cells, such as KBM5 and HCT116 cancer cell lines, curcumin can block TNFα by its action on NF-κB (Anthwal et al. 2014, Gupta et al. 2014). In particular, it modulates TNF-α expression by inhibition of the p300/CREB-specific acetyltransferase which leads to repression of acetylation of histone/non-histone proteins and therefore repression of transcription (Gupta, Tyagi, Deshmukh-Taskar, Hinojosa, Prasad and Aggarwal 2014). *In vitro* studies showed that interleukin-1β (IL-1β), TNF-α and chemokines levels can be reduced by curcumin (ABE et al. 1999, Zhang et al. 2012). Also, curcumin was found to prevent the production of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8 and IL-12 from innate immune cells. Curcumin exerts its anti-inflammatory properties via its effect on the activity of

lipoxygenase, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) enzymes (Goel, Kunnumakkara and Aggarwal 2008).

In vivo studies

There are huge animal studies confirm the anti-inflammatory effects of curcumin. Kelany et al. have reported the inhibitory effects of curcumin on TNF-α and NF-κB in metabolic syndrome rats (Kelany et al. 2017). Gong et al, have repoted that curcumin administration can improve the level of NF-κB and IL-6, MCP-1 protein expressions in the preeclampsia-like phenotype in rat model (Gong et al. 2016). Curcumin also prevents the anti-inflammatory response of synovial fibroblasts by inhibition of prostaglandin E2 (PGE2) synthesis due to COX-2 suppression in arthritis mouse model (Moon et al. 2010).

Sahebkar et al. found that curcuminoids have a significant effect on several inflammatory mediators, including IL-6, IL-8, TNFα and hs-CRP (Chrusciel, Sahebkar, Rembek-Wieliczko, Serban, Ursoniu, Mikhailidis, Jones, Mosteoru, Blaha, Martin, Rysz, Toth, Lip, Pencina, Ray, Banach, Lipid and Blood Pressure Meta-analysis Collaboration 2016, Panahi, Ghanei, Bashiri, Hajihashemi and Sahebkar 2015, Panahi, Sahebkar, Parvin and Saadat 2012, Sahebkar 2014b). Curcumin supplementation over a period of 4 weeks by healthy middle aged people has increased the activity of plasma catalase as another enzymatic antioxidant (DiSilvestro et al. 2012). In patients with rheumatoid arthritis, curcumin upregulates pro-apoptotic Bax and downregulates anti-apoptotic Bcl-2 and X-linked inhibitor of apoptosis protein (XIAP), thus inducing apoptosis and, subsequently, inhibiting the growth of synovial fibroblasts (Park et al. 2007). Chandran et al, have reported that curcumin supplementation (1 gr/day) for a perid of 8

weeks has an anti-inflammatory and antioxidant properties in patients with active rheumatoid arthritis (Chandran and Goel 2012, Kloesch, Becker, Dietersdorfer, Kiener and Steiner 2013). Curcumin supplementation can reduce serum levels of IL-8 and hs-CRP, as well as improve the quality of life in patients with sulphur mustard-induced cutaneous pruritus (Panahi, Sahebkar, Parvin and Saadat 2012). It was also reported to decrease serum concentrations of VEGF, IL-1β and IL-4 (Ganjali et al. 2014b), in obese individuals (Ganjali, Sahebkar, Mahdipour, Jamialahmadi, Torabi, Akhlaghi, Ferns, Parizadeh and Ghayour-Mobarhan 2014b). A recent meta-analysis showed that circulating CRP levels were significantly reduced by curcuminoids supplementation, depending on the duration of supplementation and the bioavailability of the curcuminoids (Sahebkar 2014a).

Curcumin effects on VEGF

Breast cancer

Breast cancer is the main cause of mortality among malignant neoplastic diseases in adult women. Curcumin is a potent anticancer agent among all spices (Liang and Hyder 2005). It has been shown that progestins can stimulate VEGF secretion in human breast cancer cells which can express progesterone receptor and mutant p53 protein (Liang et al. 2006). VEGF in turn stimulates the expression of VEGFR (Liang, Brekken and Hyder 2006), suppresses apoptosis (Hamdy 2002) and stimulates the survival of endothelial and breast tumor cells (Hamdy 2002). Therefore, inhibition of progestin-dependent secretion of VEGF can be an effective strategy to control the spread of breast cancer (Kumar et al. 2015). In this context, the polyphenol compound curcumin reduced medroxyprogesterone acetate (MPA)-induced secretion of VEGF in a dose-dependent manner from T47-D human breast cancer cells (Carroll et al. 2008).

Curcumin also significantly reduced the cell viability of MDA-MB-231 cells. In breast cancer xenografts, curcumin treatment led to a decrease in tumor volume and cell proliferation as well as inhibition of angiogenesis. Furthermore, in animal studies, there was a lower expression of VEGFR2/3 in curcumin-treated tumors, low levels of pro-angiogenic factors expression and a decrease in microvessel density (Carvalho Ferreira et al. 2015). In addition, curcumin was able to inhibit the proliferation of MDA-MB-231 cells and induce their apoptosis in vitro by inhibiting epidermal growth factor receptor (EGFR) and extracellular regulated protein kinase (ERK1/2) phosphorylation (Sun et al. 2012). Zhan Y et al. examined the combination effect of curcumin and paclitaxel in human breast cancer cell lines. This treatment showed synergistic growth inhibition (associated with decreased expression of Bcl-2 and increased expression of Bax, as well as EGFR signaling blockade) and significantly induced apoptosis (Zhan et al. 2014). Other studies curcumin inhibited cancer cell functions by disrupting the interaction between integrin and growth factor receptors. In detail, it inhibited α6β4/EGFR-dependent proliferation in A431 squamous carcinoma and MDA-MB-231 in breast carcinoma cells, thus reducing α6β4-dependent EGFR phosphorylation and the physical association between these 2 receptors (Soung and Chung 2011).

Overall, curcumin exerts multiple suppressive effects on breast carcinoma cells with pleiotropic mechanisms. Curcumin inhibits proliferation in both estrogen receptor (ER) positive MCF-7 cells and ER negative MDA-MB-231 cells. In the first case, the anti-proliferative effect was estrogen-dependent while in the second case, the effect was mediated by down-regulation of MMP-2, up-regulation of TIMP-1, inhibition of VEGF and b-FGF (Shao et al. 2002). Squires SM et al. showed that curcumin inhibits EGF-stimulated phosphorylation of EGFR,

phosphorylation of ERK1/2, nuclear factor c-fos and JNK signalling in HBL100 and MDA-MB-468 human breast cell lines (Squires et al. 2003).

VEGF is known as the most compelling angiogenic factor that its expression is regulated by NF-κB(Yoshida et al. 1997). An analog of curcumin, BDMC-A, which has more potential than curcumin in inhibiting metastatic and angiogenic pathways in breast cancer cells by modulating the expression of proteins upstream to NF-κB (such as TGF-β, TNF-α, IL-1β and c-Src) and NF-κB signaling cascade including VEGF, IL-8, c-Rel, COX-2 and MMP-9 (Mohankumar et al. 2015).

In vitro studies also reported that curcumin reduced VEGF-A expression (Thulasiraman et al. 2014). It has been shown that curcumin can significantly decrease the expression of VEGFR2/3 and inhibit angiogenesis in a murine model of human breast cancer (Carvalho Ferreira, S Arbab, Victorasso Jardim-Perassi, Ferraz Borin, RS Varma, Iskander, Shankar, M Ali and Aparecida Pires de Campos Zuccari 2015). Carroll et al. reported that VEGF levels within mammary glands of medroxyprogesterone acetate (MPA)-treated animals can be reduced by 34% following co-administration of curcumin (Carroll et al. 2009).

Figure 1 shows the effects of curcumin on VEGF and VEGF-VEFGR2 signaling pathway.

AMD

AMD is a retinal aging process, leading to irreversible blindness in the elderly (Song and Dunaief 2013). Its pathogenesis remains unclear, but oxidative stress may have a key role in the aging sequence of retina and predispose to macular degeneration (Blasiak et al. 2014). Chang et al. applied pluripotent stem cells (iPSCs) and differentiated them into RPE cells for examining the pathogenesis of AMD. They showed that curcumin can decrease ROS in AMD-RPEs as well

as the expression of several oxidative stress-regulating genes including PDGF and VEGF (Chang et al. 2014). Premanand et al. investigated mechanisms of antiangiogenic activity of curcumin on the proliferation of human retinal endothelial cells (HRECs) treated with high glucose. In these cells, currcumin induced apoptosis by regulating intracellular ROS generation, VEGF expression and release, and VEGF-mediated PKC-beta II translocation (Premanand et al. 2006). Hollborn et al. showed that although curcumin inhibited the expression and secretion of VEGF-A in a dose dependent manner, it may show adverse effects on RPE cells at different concentrations. In detail, curcumin could increase the proliferation of RPE cells at 10 μM, whereas it strongly reduced their proliferation at concentrations above 50 μM (Hollborn et al. 2013). Furthermore, curcumin supplementation at a dose of 30 mg/kg suppressed RPE–choroid protein levels of VEGF in C57BL/6N mice, thereby improving AMD-associated choroidal neovascularization (Xie et al. 2012). In a rat model of diabetes-induced retinal vascular leakage, 12-week treatment with curcumin was found to protect the retina via inhbiting calcium/calmodulin dependent protein kinase II and reducing the expression of VEGF, iNOS and intercellular adhesion molecule-1 (Li, Wang, et al. 2016).

Other cancer types and inflammatory disorders

It has been previously reported that colorectal cancers could be inhibited by diet and supplements such as curcumin (Gulbake et al. 2016). In human intestinal microvascular endothelial cells (HIMECs) stimulated with VEGF, curcumin can inhibit angiogenesis in inflammatory bowel disease (IBD) by preventing cyclo-oxygenase-2 and prostaglandin E2. Therefore, it has antiangiogenic properties and can be used as an adjuvant treatment of IBD and cancer (Binion et al. 2008). Curcumin was also reported to inhibit VEGF-A synthesis and secretion in both cell

lines of colorectal cancer HCT116 and HT-29 (Rajitha et al. 2016). Fu et al have reported that curcumin inhibited VEGF secretion from tumor cells both in porcine aortic endothelial cell line over-expressing human VEGFR2 (PAE-KDR) and in VEGF over-expressing tumor-bearing mice [162]. Curcumin suppressed phosphorylation of VEGFR2 in porcine aortic endothelial cell line over-expressing human VEGFR2 (PAE-KDR) thus indicating that it can inhibit the activation of VEGFR2 and VEGFR2 mediated signaling pathways. These results showed that curcumin can be a modulator of VEGF and VEGF-VEGFR2 signaling pathway (Fu et al. 2015a). Lin et al found an anticancer effect of curcumin for the prevention of migration and invasion in lung cancer cells. They showed that 30 μM curcumin can inhibit the expression of VEGF in human non-small cell lung cancer cells (A549) (Lin et al. 2009). Furthermore, curcumin significantly reduced cell viability in human lung squamous cell carcinoma (LSQCC cells). The upregulated genes were enriched in base excision repair (BER, such as PCNA, POLL, and MUTYH) and Janus kinase-signal transducer and activator of transcription (JAT-STAT) signaling pathways (such as AKT1 and STAT5A), while the downregulated genes were enriched in nine pathways, including the VEGF signaling pathway (such as PTK2, VEGFA, MAPK1, and MAPK14) and mitogen-activated protein kinase (MAPK) signaling pathway (ARRB2, MAPK1, MAPK14, and NFKB1) (Zhao et al. 2015).

Curcumin ameliorated fibrotic injury and sinusoidal angiogenesis in rat liver with fibrosis caused by carbon tetrachloride *via* the reduction of the expression of angiogenic markers in the fibrotic liver. In addition, curcumin inhibited VEGF expression in hepatic stellate cells (HSCs) associated with disrupting platelet-derived growth factor-β receptor (PDGF-βR)/ERK and mTOR pathways. HSC motility and vascularization were also suppressed by curcumin associated with

the blockage of PDGF-βR/focal adhesion kinase/RhoA cascade. Gain- or loss-of-function analyses revealed that activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) was required for curcumin to inhibit angiogenic properties of HSCs (Zhang et al. 2014). In rat tumor cells, curcumin treatment significantly decreased liver VEGF, CyclinD1 and CDK4 mRNA expression levels as well as CyclinD1 and CDK4 proteins levels, thus protecting the liver from the damage caused by N-nitrosodiethylamine (Huang et al. 2013).

Li et al investigated the effects of curcumin on the chemosensitivity of nephroblastoma cells. Human nephroblastoma cells line SK-NEP-1 is transplanted to the nude mice to establish the implantation tumor model of human nephroblastoma cells. An intraperitoneally injection of 30 mg/kg/d curcumin was administered into these mice 3 days a week for 4 weeks; tumor volume and serum VEGF levels were decreased in the curcumin-supplemented chemotherapy group compared with chemotherapy group (Li, Feng, et al. 2016). Dai et al. reported that liposomal curcumin can prevent hypoxia-induced angiogenesis after embolization in VX2 rabbit liver tumors (Dai, Zhang, et al. 2015). In detail, VEGF levels were decreased in tumor samples of liposomal curcumin transcatheter arterial embolization (TAE)-treated group compared with the TAE-treated group (Dai, Zhang, Shen, Chen, Liu and Gao 2015).

Hypoxia upregulates multiple pro-angiogenic pathways thus promoting the growth of endothelial, stromal and vascular cells (Krock, Skuli and Simon 2011). Furthermore, hypoxia influences vessel patterning, maturation, and function. Hypoxia-inducible factors (HIFs) are transcription factors that regulate angiogenesis by the expression of several metabolic, angiogenic and cell cycle genes (Krock, Skuli and Simon 2011). VEGF is one of the primary target genes for HIFs (Ramakrishnan et al. 2014). Curcumin has been reported to exert

anticancer properties via inhibition of the HIF pathway. In this context, Dai et al. reported that liposomal curcumin can prevent hypoxia-induced angiogenesis after embolization in VX2 rabbit liver tumors (Dai, Zhang, Shen, Chen, Liu and Gao 2015). In detail, VEGF levels were decreased in tumor samples of liposomal curcumin transcatheter arterial embolization (TAE)-treated group compared with the TAE-treated group (Dai, Zhang, Shen, Chen, Liu and Gao 2015). Furthermore, curcumin was shown to suppress the upregulation of hypoxia-induced ROS as well as the production of HIF-1αin K1 papillary thyroid cancer cells, thus inhibiting tumor migration (Tan et al. 2015). Similarly, curcumin downregulated HIF-1α in pancreatic cancer cells as well as in hepatocellular, oral squamous and breast carcinoma cells (Duan et al. 2014, Nagaraju et al. 2015, Strofer et al. 2011). Curcumin may also protect from the toxic effects of hypoxia other cell types such as adipocytes and hepatocytes (in the presence of liver fibrosis) (Priyanka et al. 2014, Yao et al. 2013). In vitro, in vivo and clinical studies evaluating the effects of curcumin on VEGF are summarized in **Table 2** and **Table 3**. Studies evaluating the effects of curcumin on VEGF levels in retinal disorders are summarized in **Table 4**.

Clinical Trials

Three studies in human subjects evaluated the effectiveness of curcumin supplementation on VEGF levels. In the first small trial by Ganjali et al., 1 g/day curcumin supplementation for a period of 4 weeks led to improved serum VEGF levels in obese individuals (Ganjali, Sahebkar, Mahdipour, Jamialahmadi, Torabi, Akhlaghi, Ferns, Parizadeh and Ghayour-Mobarhan 2014b). Wolff et al. reported that VEGF concentrations were not affected by curcumin in patients with pediatric brain tumors (Wolff et al. 2012). In another trial, curcumin supplementation significantly reduced VEGF levels by 30% in patients with advanced and metastatic breast

cancer. Moreover, the maximal tolerated dose of curcumin was 8,000 mg/d, in combination with docetaxel (100 mg/m^2) administered every 3 weeks for 6 cycles (Bayet-Robert et al. 2010).

Conclusions

Angiogenesis, the formation of new blood vessels from existing host vasculature, is an important pathogenetic factor in tumor growth, metastasis and other diseases including AMD, autoimmune and cardiovascular diseases. Curcumin was shown to inhibit carcinogenesis by downregulation of angiogenic mediators such as VEGF and fibroblast growth factor (FGF). The anti-angiogenic activity of curcumin is basically mediated by its inhibitory effect on NF-κB transcription. Curcumin further inhibits the matrix metallopreoteases, plasminogen activator and cell adhesion molecules culminating in inhibition of angiogenesis. The effect of curcumin on the overall process of angiogenesis expands its potential as an anti-angiogenic drug. Curcumin can decrease serum concentrations of VEGF, IL-1β and IL-4 in obese individuals as well as VEGF levels in colorectal, lung and liver cancers. Curcumin may also reduce ROS in AMD-RPEs as well as the expression of PDGF and VEGF genes. The expression and secretion of VEGF-A can be decreased by curcumin in a dose dependent manner, but adverse effects on RPE cells may occur at different concentrations. Inhibition of progestin-dependent secretion of VEGF is an effective strategy to control breast cancer spread. VEGF is the most compelling angiogenic factor that its expression is regulated by NF-κB. Curcumin can inhibit metastatic and angiogenic pathways in breast cancer cells by modulating the expression of proteins upstream to NF-κB and NF-κB signaling cascade including VEGF.

Despite several lines of in vitro and preclinical evidence, only a few randomized clinical trials exist to show the positive therapeutic effects of curcumin on VEGF levels, leading to

improvements in breast cancer and retinal diseases. Further human trials are needed to evaluate the pharmacotherapeutic properties of curcumin on circulating VEGF levels and establish its clinical implications.

Conflict of interests

Niki Katsiki has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and WinMedica. Muhammed Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

References

Abdel-Daim MM, Abdou RH. 2015. Protective effects of diallyl sulfide and curcumin separately against thallium-induced toxicity in rats. Cell Journal (Yakhteh).17:379.

Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A. 2017. Therapeutic Effects of Curcumin in Inflammatory and Immune-Mediated Diseases: A Nature-Made Jack-of-All-Trades? Journal of cellular physiology. Jan 06.

ABE Y, Hashimoto S, HORIE T. 1999. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. Pharmacological research.39:41-47.

Advani SH. 2010. Targeting mTOR pathway: A new concept in cancer therapy. Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology. Oct;31:132-136.

Aflibercept (Eylea): Treatment of Neovascular (Wet) Age-Related Macular Degeneration (wAMD). 2015. Ottawa ON: Cadth 2015.

Aggarwal BB. 2010. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annual review of nutrition. Aug 21;30:173-199.

Aggarwal BB, Harikumar KB. 2009. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. The international journal of biochemistry & cell biology. Jan;41:40-59.

Akman A, Yilmaz E, Mutlu H, Ozdogan M. 2009. Complete remission of psoriasis following bevacizumab therapy for colon cancer. Clinical and experimental dermatology.34:e202-e204.

Alitalo K, Carmeliet P. 2002. Molecular mechanisms of lymphangiogenesis in health and disease. Cancer cell.1:219-227.

Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. 2007. Bioavailability of curcumin: problems and promises. Molecular pharmaceutics.4:807-818.

Anand P, Sung B, Kunnumakkara AB, Rajasekharan KN, Aggarwal BB. 2011. Suppression of pro-inflammatory and proliferative pathways by diferuloylmethane (curcumin) and its analogues dibenzoylmethane, dibenzoylpropane, and dibenzylideneacetone: role of Michael acceptors and Michael donors. Biochemical pharmacology.82:1901.

Anthwal A, Thakur BK, Rawat MS, Rawat DS, Tyagi AK, Aggarwal BB. 2014. Synthesis, characterization and in vitro anticancer activity of C-5 curcumin analogues with potential to inhibit TNF-alpha-induced NF-kappaB activation. BioMed research international.2014:524161.

Basnet P, Skalko-Basnet N. 2011. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules. Jun 03;16:4567-4598.

Bayet-Robert M, Kwiatowski F, Leheurteur M, Gachon F, Planchat E, Abrial C, Mouret-Reynier M-A, Durando X, Barthomeuf C, Chollet P. 2010. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. Cancer biology & therapy.9:8-14.

Bianchi E, Scarinci F, Grande C, Plateroti R, Plateroti P, Plateroti A, Fumagalli L, Capozzi P, Feher J, Artico M. 2012. Immunohistochemical Profile and VEGF, TGF-β and PGE2 in Human Pterygium and Normal Conjunctiva: Experimental Study and Review of the Literature. International journal of immunopathology and pharmacology.25:607-615.

Binion DG, Otterson MF, Rafiee P. 2008. Curcumin inhibits VEGF-mediated angiogenesis in human intestinal microvascular endothelial cells through COX-2 and MAPK inhibition. Gut.57:1509-1517.

Bishnoi M, Chopra K, Rongzhu L, Kulkarni SK. 2011. Protective effect of curcumin and its combination with piperine (bioavailability enhancer) against haloperidol-associated neurotoxicity: cellular and neurochemical evidence. Neurotoxicity research.20:215-225.
Blasiak J, Petrovski G, Veréb Z, Facskó A, Kaarniranta K. 2014. Oxidative stress, hypoxia, and autophagy in the neovascular processes of age-related macular degeneration. BioMed research international.2014.
Brenchley P. 2000. Angiogenesis in inflammatory joint disease: a target for therapeutic intervention. Clinical & Experimental Immunology.121:426-429.
Brondino N, Re S, Boldrini A, Cuccomarino A, Lanati N, Barale F, Politi P. 2014. Curcumin as a therapeutic agent in dementia: a mini systematic review of human studies. The Scientific World Journal.2014.
Bry M, Kivelä R, Holopainen T, Anisimov A, Tammela T, Soronen J, Silvola J, Saraste A, Jeltsch M, Korpisalo P. 2010. Vascular endothelial growth factor-B acts as a coronary growth factor in transgenic rats without inducing angiogenesis, vascular leak, or inflammation. Circulation.122:1725-1733.
Cao J, Liu Y, Jia L, Jiang LP, Geng CY, Yao XF, Kong Y, Jiang BN, Zhong LF. 2008. Curcumin attenuates acrylamide-induced cytotoxicity and genotoxicity in HepG2 cells by ROS scavenging. Journal of agricultural and food chemistry. Dec 24;56:12059-12063.
Carroll CE, Benakanakere I, Besch-Williford C, Ellersieck MR, Hyder SM. 2009. Curcumin delays development of medroxyprogesterone acetate-accelerated 7, 12-dimethylbenz [a] anthracene-induced mammary tumors. Menopause (New York, NY).17:178-184.
Carroll CE, Ellersieck MR, Hyder SM. 2008. Curcumin inhibits MPA-induced secretion of VEGF from T47-D human breast cancer cells. Menopause.15:570-574.
Carroll CE, Liang Y, Benakanakere I, Besch-Williford C, Hyder SM. 2013. The anticancer agent YC-1 suppresses progestin-stimulated VEGF in breast cancer cells and arrests breast tumor development. International journal of oncology. Jan;42:179-187.
Carvalho Ferreira L, S Arbab A, Victorasso Jardim-Perassi B, Ferraz Borin T, RS Varma N, Iskander A, Shankar A, M Ali M, Aparecida Pires de Campos Zuccari D. 2015. Effect of curcumin on pro-angiogenic factors in the xenograft model of breast cancer. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents).15:1285-1296.
Chakraborty G, Jain S, Kale S, Raja R, Kumar S, Mishra R, Kundu GC. 2008. Curcumin suppresses breast tumor angiogenesis by abrogating osteopontin-induced VEGF expression. Mol Med Rep.1:641-646.
Chandran B, Goel A. 2012. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytotherapy research: PTR. Nov;26:1719-1725.
Chang Y-C, Chang W-C, Hung K-H, Yang D-M, Cheng Y-H, Liao Y-W, Woung L-C, Tsai C-Y, Hsu C-C, Lin T-C. 2014. The generation of induced pluripotent stem cells for macular degeneration as a drug screening platform: identification of curcumin as a protective agent for retinal pigment epithelial cells against oxidative stress. Frontiers in aging neuroscience.6:191.
Chen SS, MIChAel A, Butler-Manuel SA. 2012a. Advances in the Treatment of Ovarian Cancer—A Potential Role of Anti-inflammatory Phytochemicals. Discovery medicine.13:7-17.
Chin D, Huebbe P, Pallauf K, Rimbach G. 2013. Neuroprotective properties of curcumin in Alzheimer's disease-merits and limitations. Current medicinal chemistry.20:3955-3985.
Chrusciel P, Sahebkar A, Rembek-Wieliczko M, Serban MC, Ursoniu S, Mikhailidis DP, Jones SR, Mosteoru S, Blaha MJ, Martin SS, et al. 2016. Impact of statin therapy on plasma adiponectin concentrations: A systematic review and meta-analysis of 43 randomized controlled trial arms. Atherosclerosis. Oct;253:194-208.
Claesson-Welsh L. 2003. Signal transduction by vascular endothelial growth factor receptors. In: Portland Press Limited.

Clauss M, Gerlach M, Gerlach H, Brett J, Wang F, Familletti P, Pan Y, Olander J, Connolly D, Stern D. 1990. Vascular permeability factor: a tumor-derived polypeptide that induces endothelial cell and monocyte procoagulant activity, and promotes monocyte migration. The Journal of experimental medicine.172:1535-1545.

Cohen MH, Gootenberg J, Keegan P, Pazdur R. 2007. FDA drug approval summary: bevacizumab (Avastin®) plus carboplatin and paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. The Oncologist.12:713-718.

Dai C, Tang S, Li D, Zhao K, Xiao X. 2015a. Curcumin attenuates quinocetone-induced oxidative stress and genotoxicity in human hepatocyte L02 cells. Toxicology mechanisms and methods.25:340-346.

Dai F, Zhang X, Shen W, Chen J, Liu L, Gao G. 2015. liposomal curcumin inhibits hypoxia-induced angiogenesis after transcatheter arterial embolization in VX2 rabbit liver tumors. OncoTargets and therapy.8:2601.

Decio A, Cesca M, Bizzaro F, Porcu L, Bettolini R, Ubezio P, Taraboletti G, Belotti D, Giavazzi R. 2015a. Cediranib combined with chemotherapy reduces tumor dissemination and prolongs the survival of mice bearing patient-derived ovarian cancer xenografts with different responsiveness to cisplatin. Clin Exp Metastasis. Oct;32:647-658.

DiSilvestro RA, Joseph E, Zhao S, Bomser J. 2012. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutrition journal.11:1.

Duan W, Chang Y, Li R, Xu Q, Lei J, Yin C, Li T, Wu Y, Ma Q, Li X. 2014. Curcumin inhibits hypoxia inducible factor1alphainduced epithelialmesenchymal transition in HepG2 hepatocellular carcinoma cells. Mol Med Rep. Nov;10:2505-2510.

Dunbar JA, Reddy P, Davis-Lameloise N, Philpot B, Laatikainen T, Kilkkinen A, Bunker SJ, Best JD, Vartiainen E, Lo SK. 2008. Depression: an important comorbidity with metabolic syndrome in a general population. Diabetes care.31:2368-2373.

Epstein J, Sanderson IR, MacDonald TT. 2010. Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. British journal of nutrition.103:1545-1557.

Esmaily H, Sahebkar A, Iranshahi M, Ganjali S, Mohammadi A, Ferns G, Ghayour-Mobarhan M. 2015a. An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial. Chinese journal of integrative medicine.21:332-338.

Farhangi B, Alizadeh AM, Khodayari H, Khodayari S, Dehghan MJ, Khori V, Heidarzadeh A, Khaniki M, Sadeghiezadeh M, Najafi F. 2015. Protective effects of dendrosomal curcumin on an animal metastatic breast tumor. European journal of pharmacology.758:188-196.

Ferrara N. 2004. Vascular endothelial growth factor: basic science and clinical progress. Endocrine reviews.25:581-611.

Ferrara N, Gerber H-P, LeCouter J. 2003a. The biology of VEGF and its receptors. Nature medicine.9:669-676.

Folkman J. The role of angiogenesis in tumor growth. Proceedings of the Seminars in cancer biology; 1992.

Folkman J, Shing Y. 1992. Angiogenesis. The Journal of biological chemistry. Jun 05;267:10931-10934. Epub 1992/06/05.

Fu Z, Chen X, Guan S, Yan Y, Lin H, Hua ZC. 2015b. Curcumin inhibits angiogenesis and improves defective hematopoiesis induced by tumor-derived VEGF in tumor model through modulating VEGF-VEGFR2 signaling pathway. Oncotarget. Aug 14;6:19469-19482.

Ganjali S, Blesso CN, Banach M, Pirro M, Majeed M, Sahebkar A. 2017. Effects of curcumin on HDL functionality. Pharmacological research. Feb 10;119:208-218.

Ganjali S, Sahebkar A, Mahdipour E, Jamialahmadi K, Torabi S, Akhlaghi S, Ferns G, Parizadeh SM, Ghayour-Mobarhan M. 2014a. Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. TheScientificWorldJournal.2014:898361.
Ghandadi M, Sahebkar A. 2016. Curcumin: An effective inhibitor of interleukin-6. Current pharmaceutical design. Oct 06.
Goel A, Kunnumakkara AB, Aggarwal BB. 2008. Curcumin as "Curecumin": from kitchen to clinic. Biochemical pharmacology.75:787-809.
Gong P, Liu M, Hong G, Li Y, Xue P, Zheng M, Wu M, Shen L, Yang M, Diao Z, et al. 2016. Curcumin improves LPS-induced preeclampsia-like phenotype in rat by inhibiting the TLR4 signaling pathway. Placenta. May;41:45-52.
Gulbake A, Jain A, Jain A, Jain A, Jain SK. 2016. Insight to drug delivery aspects for colorectal cancer. World journal of gastroenterology.22:582.
Gupta SC, Patchva S, Aggarwal BB. 2013. Therapeutic roles of curcumin: lessons learned from clinical trials. The AAPS journal. Jan;15:195-218.
Gupta SC, Tyagi AK, Deshmukh-Taskar P, Hinojosa M, Prasad S, Aggarwal BB. 2014. Downregulation of tumor necrosis factor and other proinflammatory biomarkers by polyphenols. Archives of biochemistry and biophysics. Oct 01;559:91-99.
Hamdy RC. 2002. Lessons learned from the Women's Health Initiative study. Southern medical journal. Sep;95:951-952. Epub 2002/10/03.
Han ES, Monk BJ. 2007. Bevacizumab in the treatment of ovarian cancer. Expert review of anticancer therapy.7:1339-1345.
Hartnett ME. 2014. Vascular endothelial growth factor antagonist therapy for retinopathy of prematurity. Clinics in perinatology. Dec;41:925-943. Epub 2014/12/03.
Heckman CA, Holopainen T, Wirzenius M, Keskitalo S, Jeltsch M, Ylä-Herttuala S, Wedge SR, Jürgensmeier JM, Alitalo K. 2008. The tyrosine kinase inhibitor cediranib blocks ligand-induced vascular endothelial growth factor receptor-3 activity and lymphangiogenesis. Cancer Research.68:4754-4762.
Hoesel B, Schmid JA. 2013. The complexity of NF-kappaB signaling in inflammation and cancer. Molecular cancer. Aug 02;12:86.
Hollborn M, Chen R, Wiedemann P, Reichenbach A, Bringmann A, Kohen L. 2013. Cytotoxic effects of curcumin in human retinal pigment epithelial cells. PloS one.8:e59603.
Houck KA, Leung D, Rowland A, Winer J, Ferrara N. 1992. Dual regulation of vascular endothelial growth factor bioavailability by genetic and proteolytic mechanisms. Journal of Biological Chemistry.267:26031-26037.
Huang CZ, Huang WZ, Zhang G, Tang DL. 2013. In vivo study on the effects of curcumin on the expression profiles of anti-tumour genes (VEGF, CyclinD1 and CDK4) in liver of rats injected with DEN. Molecular biology reports.40:5825-5831.
Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E. 2004. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. New England journal of medicine.350:2335-2342.
Iqbal M, Sharma SD, Okazaki Y, Fujisawa M, Okada S. 2003. Dietary supplementation of curcumin enhances antioxidant and phase II metabolizing enzymes in ddY male mice: possible role in protection against chemical carcinogenesis and toxicity. Pharmacology & toxicology.92:33-38.
Ireson CR, Jones DJ, Orr S, Coughtrie MW, Boocock DJ, Williams ML, Farmer PB, Steward WP, Gescher AJ. 2002. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiology and Prevention Biomarkers.11:105-111.

Jeong GS, Oh GS, Pae HO, Jeong SO, Kim YC, Shin MK, Seo BY, Han SY, Lee HS, Jeong JG, et al. 2006. Comparative effects of curcuminoids on endothelial heme oxygenase-1 expression: ortho-methoxy groups are essential to enhance heme oxygenase activity and protection. Experimental & molecular medicine. Aug 31;38:393-400.
Jeong SJ, Koh W, Lee EO, Lee HJ, Lee HJ, Bae H, Lu J, Kim SH. 2011. Antiangiogenic phytochemicals and medicinal herbs. Phytotherapy research: PTR. Jan;25:1-10.
Ji R-R, Gereau RW, Malcangio M, Strichartz GR. 2009. MAP kinase and pain. Brain research reviews.60:135-148.
Jin J, Sison K, Li C, Tian R, Wnuk M, Sung H-K, Jeansson M, Zhang C, Tucholska M, Jones N. 2012. Soluble FLT1 binds lipid microdomains in podocytes to control cell morphology and glomerular barrier function. Cell.151:384-399.
Jurenka JS. 2009. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative medicine review: a journal of clinical therapeutic. Jun;14:141-153.
Karimian MS, Pirro M, Johnston TP, Majeed M, Sahebkar A. 2017. Curcumin and Endothelial Function: Evidence and Mechanisms of Protective Effects. Current pharmaceutical design. Feb 22.
Karimian MS, Pirro M, Majeed M, Sahebkar A. 2017. Curcumin as a natural regulator of monocyte chemoattractant protein-1. Cytokine & growth factor reviews. Feb;33:55-63.
Kelany ME, Hakami TM, Omar AH. 2017. Curcumin improves the metabolic syndrome in high-fructose-diet-fed rats: role of TNF-alpha, NF-kappaB, and oxidative stress. Canadian journal of physiology and pharmacology. Feb;95:140-150.
Kiselyov A, Balakin KV, Tkachenko SE. 2007. VEGF/VEGFR signalling as a target for inhibiting angiogenesis. Expert opinion on investigational drugs.16:83-107.
Kloesch B, Becker T, Dietersdorfer E, Kiener H, Steiner G. 2013. Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes. International immunopharmacology. Feb;15:400-405.
Koch S, Tugues S, Li X, Gualandi L, Claesson-Welsh L. 2011. Signal transduction by vascular endothelial growth factor receptors. Biochemical Journal.437:169-183.
Krock BL, Skuli N, Simon MC. 2011. Hypoxia-induced angiogenesis: good and evil. Genes & cancer. Dec;2:1117-1133.
Kumar P, Kadakol A, Krishna Shasthrula P, Arunrao Mundhe N, Sudhir Jamdade V, C Barua C, Bhanudas Gaikwad A. 2015. Curcumin as an adjuvant to breast cancer treatment. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents).15:647-656.
Kunnumakkara AB, Anand P, Aggarwal BB. 2008. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett. Oct 08;269:199-225.
Lee KW, Kim J-H, Lee HJ, Surh Y-J. 2005. Curcumin inhibits phorbol ester-induced up-regulation of cyclooxygenase-2 and matrix metalloproteinase-9 by blocking ERK1/2 phosphorylation and NF-κB transcriptional activity in MCF10A human breast epithelial cells. Antioxidants & redox signaling.7:1612-1620.
Lelli D, Sahebkar A, Johnston TP, Pedone C. 2017. Curcumin use in pulmonary diseases: State of the art and future perspectives. Pharmacological research. Jan;115:133-148.
Li J, Wang P, Ying J, Chen Z, Yu S. 2016. Curcumin Attenuates Retinal Vascular Leakage by Inhibiting Calcium/Calmodulin-Dependent Protein Kinase II Activity in Streptozotocin-Induced Diabetes. Cellular Physiology and Biochemistry.39:1196-1208.

Li X-Y, Feng Y-Y, Dan W, Pan D, Zhang G-F, Wang X-L, Hou G-J. 2016. Study on the influence of curcumin on chemosensitivity of nephroblastoma cells. Asian Pacific journal of tropical medicine.9:801-805.
Liang Y, Brekken RA, Hyder SM. 2006. Vascular endothelial growth factor induces proliferation of breast cancer cells and inhibits the anti-proliferative activity of anti-hormones. Endocrine-related cancer.13:905-919.
Liang Y, Hyder SM. 2005. Proliferation of endothelial and tumor epithelial cells by progestin-induced vascular endothelial growth factor from human breast cancer cells: paracrine and autocrine effects. Endocrinology.146:3632-3641.
Lin JK, Lin-Shiau SY. 2001. Mechanisms of cancer chemoprevention by curcumin. Proceedings of the National Science Council, Republic of China Part B, Life sciences. Apr;25:59-66.
Lin S-S, Lai K-C, Hsu S-C, Yang J-S, Kuo C-L, Lin J-P, Ma Y-S, Wu C-C, Chung J-G. 2009. Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and-9 and Vascular Endothelial Growth Factor (VEGF). Cancer letters.285:127-133.
Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D, Zhai G. 2016. Oral bioavailability of curcumin: problems and advancements. Journal of drug targeting. Sep;24:694-702.
Luo L, Uehara H, Zhang X, Das SK, Olsen T, Holt D, Simonis JM, Jackman K, Singh N, Miya TR. 2013. Photoreceptor avascular privilege is shielded by soluble VEGF receptor-1. Elife.2:e00324.
Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. 2006. Multiple biological activities of curcumin: a short review. Life sciences.78:2081-2087.
Manolova Y, Deneva V, Antonov L, Drakalska E, Momekova D, Lambov N. 2014. The effect of the water on the curcumin tautomerism: A quantitative approach. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy.132:815-820.
Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. 2012. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer metastasis reviews. Jun;31:143-162.
Mintz-Hittner HA. 2012. Treatment of retinopathy of prematurity with vascular endothelial growth factor inhibitors. Early human development.88:937-941.
Mirzaei H, Naseri G, Rezaee R, Mohammadi M, Banikazemi Z, Mirzaei HR, Salehi H, Peyvandi M, Pawelek JM, Sahebkar A. 2016. Curcumin: A new candidate for melanoma therapy? International journal of cancer. Oct 15;139:1683-1695.
Mirzaei H, Shakeri A, Rashidi B, Jalili A, Banikazemi Z, Sahebkar A. 2017. Phytosomal curcumin: A review of pharmacokinetic, experimental and clinical studies. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. Jan;85:102-112.
Mohammadi A, Sahebkar A, Iranshahi M, Amini M, Khojasteh R, Ghayour-Mobarhan M, Ferns GA. 2013. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytotherapy research: PTR. Mar;27:374-379.
Mohankumar K, Sridharan S, Pajaniradje S, Singh VK, Ronsard L, Banerjea AC, Somasundaram DB, Coumar MS, Periyasamy L, Rajagopalan R. 2015. BDMC-A, an analog of curcumin, inhibits markers of invasion, angiogenesis, and metastasis in breast cancer cells via NF-κB pathway—A comparative study with curcumin. Biomedicine & Pharmacotherapy.74:178-186.
Momtazi AA, Derosa G, Maffioli P, Banach M, Sahebkar A. 2016. Role of microRNAs in the Therapeutic Effects of Curcumin in Non-Cancer Diseases. Molecular diagnosis & therapy. Aug;20:335-345.
Momtazi AA, Sahebkar A. 2016. Difluorinated Curcumin: A Promising Curcumin Analogue with Improved Anti-Tumor Activity and Pharmacokinetic Profile. Current pharmaceutical design.22:4386-4397.

Momtazi AA, Shahabipour F, Khatibi S, Johnston TP, Pirro M, Sahebkar A. 2016. Curcumin as a MicroRNA Regulator in Cancer: A Review. Reviews of physiology, biochemistry and pharmacology.171:1-38.
Moon DO, Kim MO, Choi YH, Park YM, Kim GY. 2010. Curcumin attenuates inflammatory response in IL-1beta-induced human synovial fibroblasts and collagen-induced arthritis in mouse model. International immunopharmacology. May;10:605-610.
Nagaraju GP, Zhu S, Ko JE, Ashritha N, Kandimalla R, Snyder JP, Shoji M, El-Rayes BF. 2015. Antiangiogenic effects of a novel synthetic curcumin analogue in pancreatic cancer. Cancer Lett. Feb 28;357:557-565.
Nagpal M, Sood S. 2013. Role of curcumin in systemic and oral health: An overview. Journal of natural science, biology, and medicine. Jan;4:3-7.
Narayanan S, Callis-Duffin K, Batten J, Agarwal N. 2010. Improvement of psoriasis during sunitinib therapy for renal cell carcinoma. The American journal of the medical sciences.339:580-581.
Nguyen TA, Friedman AJ. 2013. Curcumin: a novel treatment for skin-related disorders. Journal of drugs in dermatology: JDD. Oct;12:1131-1137.
Niu G, Chen X. 2010. Vascular endothelial growth factor as an anti-angiogenic target for cancer therapy. Current drug targets. Aug;11:1000-1017.
Pajusola K, Aprelikova O, Pelicci G, Weich H, Claesson-Welsh L, Alitalo K. 1994. Signalling properties of FLT4, a proteolytically processed receptor tyrosine kinase related to two VEGF receptors. Oncogene.9:3545-3555.
Pan M-H, Huang T-M, Lin J-K. 1999. Biotransformation of curcumin through reduction and glucuronidation in mice. Drug metabolism and disposition.27:486-494.
Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A. 2016. Curcumin as a Potential Candidate for Treating Hyperlipidemia: A Review of Cellular and Metabolic Mechanisms. Journal of cellular physiology. Dec 24.
Panahi Y, Alishiri GH, Parvin S, Sahebkar A. 2016. Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial. Journal of dietary supplements.13:209-220.
Panahi Y, Badeli R, Karami GR, Sahebkar A. 2015. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. Phytotherapy research: PTR. Jan;29:17-21.
Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A. 2015. Short-term Curcuminoid Supplementation for Chronic Pulmonary Complications due to Sulfur Mustard Intoxication: Positive Results of a Randomized Double-blind Placebo-controlled Trial. Drug research. Nov;65:567-573. Epub 2014/10/01.
Panahi Y, Hosseini MS, Khalili N, Naimi E, Simental-Mendia LE, Majeed M, Sahebkar A. 2016. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. Aug;82:578-582.
Panahi Y, Hosseini MS, Khalili N, Naimi E, Soflaei SS, Majeed M, Sahebkar A. 2016. Effects of supplementation with curcumin on serum adipokine concentrations: A randomized controlled trial. Nutrition. Oct;32:1116-1122.
Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A. 2014. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. Complementary therapies in medicine. Oct;22:851-857.

Panahi Y, Khalili N, Sahebi E, Namazi S, Karimian MS, Majeed M, Sahebkar A. 2017. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. Inflammopharmacology. Feb;25:25-31.
Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendia LE, Sahebkar A. 2016. Curcumin Lowers Serum Lipids and Uric Acid in Subjects With Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial. Journal of cardiovascular pharmacology. Sep;68:223-229.
Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. 2014a. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytotherapy research: PTR. Nov;28:1625-1631.
Panahi Y, Saadat A, Beiraghdar F, Sahebkar A. 2014. Adjuvant Therapy with Bioavailability-Boosted Curcuminoids Suppresses Systemic Inflammation and Improves Quality of Life in Patients with Solid Tumors: A Randomized Double-Blind Placebo-Controlled Trial. Phytotherapy Research.28:1461-1467.
Panahi Y, Sahebkar A, Amiri M, Davoudi SM, Beiraghdar F, Hoseininejad SL, Kolivand M. 2012. Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. The British journal of nutrition. Oct;108:1272-1279.
Panahi Y, Sahebkar A, Parvin S, Saadat A. 2012. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. Annals of clinical biochemistry. Nov;49:580-588. Epub 2012/10/06.
Park C, Moon DO, Choi IW, Choi BT, Nam TJ, Rhu CH, Kwon TK, Lee WH, Kim GY, Choi YH. 2007. Curcumin induces apoptosis and inhibits prostaglandin E(2) production in synovial fibroblasts of patients with rheumatoid arthritis. International journal of molecular medicine. Sep;20:365-372.
Pertl L, Steinwender G, Mayer C, Hausberger S, Pöschl E-M, Wackernagel W, Wedrich A, El-Shabrawi Y, Haas A. 2015. A systematic review and meta-analysis on the safety of vascular endothelial growth factor (VEGF) inhibitors for the treatment of retinopathy of prematurity. PloS one.10:e0129383.
Premanand C, Rema M, Sameer MZ, Sujatha M, Balasubramanyam M. 2006. Effect of curcumin on proliferation of human retinal endothelial cells under in vitro conditions. Investigative ophthalmology & visual science.47:2179-2184.
Priyanka A, Anusree SS, Nisha VM, Raghu KG. 2014. Curcumin improves hypoxia induced dysfunctions in 3T3-L1 adipocytes by protecting mitochondria and down regulating inflammation. BioFactors. Sep-Oct;40:513-523.
Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramirez-Tortosa M. 2016. Curcumin and health. Molecules.21:264.
Rahmani S, Asgary S, Askari G, Keshvari M, Hatamipour M, Feizi A, Sahebkar A. 2016. Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial. Phytotherapy research: PTR. Sep;30:1540-1548.
Rajitha B, Nagaraju GP, Shaib WL, Alese OB, Snyder JP, Shoji M, Pattnaik S, Alam A, El-Rayes BF. 2016. Novel synthetic curcumin analogs as potent antiangiogenic agents in colorectal cancer. Molecular carcinogenesis.
Ramakrishnan S, Anand V, Roy S. 2014. Vascular endothelial growth factor signaling in hypoxia and inflammation. Journal of neuroimmune pharmacology: the official journal of the Society on NeuroImmune Pharmacology. Mar;9:142-160.
Ramezani M, Hatamipour M, Sahebkar A. 2017. Promising Anti-tumor properties of Bisdemethoxycurcumin: A Naturally Occurring Curcumin Analogue. Journal of cellular physiology. Jan 11.

Ravindran J, Prasad S, Aggarwal BB. 2009. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? The AAPS journal. Sep;11:495-510.
Recio MC, Andujar I, Rios JL. 2012. Anti-inflammatory agents from plants: progress and potential. Curr Med Chem.19:2088-2103.
Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. 2010. Oxidative stress, inflammation, and cancer: how are they linked? Free radical biology & medicine. Dec 01;49:1603-1616.
Roskoski R. 2005. Src kinase regulation by phosphorylation and dephosphorylation. Biochemical and biophysical research communications.331:1-14.
Ruby A, Kuttan G, Babu KD, Rajasekharan K, Kuttan R. 1995. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer letters.94:79-83.
Ruscito I, Gasparri ML, Marchetti C, De Medici C, Bracchi C, Palaia I, Imboden S, Mueller MD, Papadia A, Muzii L. 2016. Cediranib in ovarian cancer: state of the art and future perspectives. Tumor Biology.37:2833-2839.
Sahebkar A. 2010. Molecular mechanisms for curcumin benefits against ischemic injury. Fertility and sterility. Oct;94:e75-76; author reply e77.
Sahebkar A. 2013. Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? BioFactors. Mar-Apr;39:197-208.
Sahebkar A. 2014a. Are Curcuminoids Effective C-Reactive Protein-Lowering Agents in Clinical Practice? Evidence from a Meta-Analysis. Phytotherapy research.28:633-642.
Sahebkar A. 2014b. Curcuminoids for the management of hypertriglyceridaemia. Nature reviews Cardiology. Feb;11:123.
Sahebkar A, Henrotin Y. 2016. Analgesic Efficacy and Safety of Curcuminoids in Clinical Practice: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain medicine. Jun;17:1192-1202.
Sahebkar A, Mohammadi A, Atabati A, Rahiman S, Tavallaie S, Iranshahi M, Akhlaghi S, Ferns GA, Ghayour-Mobarhan M. 2013. Curcuminoids modulate pro-oxidant-antioxidant balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. Phytotherapy research: PTR. Dec;27:1883-1888.
Sahebkar A, Saboni N, Pirro M, Banach M. 2017. Curcumin: An effective adjunct in patients with statin-associated muscle symptoms? Journal of cachexia, sarcopenia and muscle. Feb;8:19-24.
Sethi G, Sung B, Aggarwal BB. 2008. Nuclear factor-kappaB activation: from bench to bedside. Experimental biology and medicine. Jan;233:21-31.
Shao ZM, Shen ZZ, Liu CH, Sartippour MR, Go VL, Heber D, Nguyen M. 2002. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. International Journal of Cancer.98:234-240.
Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, Marczylo TH, Morgan B, Hemingway D, Plummer SM. 2004. Phase I clinical trial of oral curcumin. Clinical Cancer Research.10:6847-6854.
Shibuya M. 2011a. Involvement of Flt-1 (VEGF receptor-1) in cancer and preeclampsia. Proceedings of the Japan Academy, Series B.87:167-178.
Shibuya M. 2011b. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. Genes & cancer. Dec;2:1097-1105.
Shibuya M. 2014. VEGF-VEGFR signals in health and disease. Biomol Ther (Seoul).22:1-9.
Shibuya M, Claesson-Welsh L. 2006. Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. Experimental cell research.312:549-560.

Shinkaruk S, Bayle M, Lain G, Deleris G. 2003. Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy. Current Medicinal Chemistry-Anti-Cancer Agents.3:95-117.
Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas P. 1998. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta medica.64:353-356.
Song D, Dunaief JL. 2013. Retinal iron homeostasis in health and disease. Frontiers in aging neuroscience.5:24.
Soung YH, Chung J. 2011. Curcumin inhibition of the functional interaction between integrin α6β4 and the epidermal growth factor receptor. Molecular cancer therapeutics.10:883-891.
Squires MS, Hudson EA, Howells L, Sale S, Houghton CE, Jones JL, Fox LH, Dickens M, Prigent SA, Manson MM. 2003. Relevance of mitogen activated protein kinase (MAPK) and phosphotidylinositol-3-kinase/protein kinase B (PI3K/PKB) pathways to induction of apoptosis by curcumin in breast cells. Biochemical pharmacology.65:361-376.
Strofer M, Jelkmann W, Depping R. 2011. Curcumin decreases survival of Hep3B liver and MCF-7 breast cancer cells: the role of HIF. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al]. Jul;187:393-400.
Sun X-D, Liu X-E, Huang D-S. 2012. Curcumin induces apoptosis of triple-negative breast cancer cells by inhibition of EGFR expression. Molecular medicine reports.6:1267-1270.
Tagawa T, Morgan R, Yen Y, Mortimer J. 2011. Ovarian cancer: opportunity for targeted therapy. Journal of oncology.2012.
Takahashi S. 2011. Vascular endothelial growth factor (VEGF), VEGF receptors and their inhibitors for antiangiogenic tumor therapy. Biological and Pharmaceutical Bulletin.34:1785-1788.
Tammela T, Zarkada G, Wallgard E, Murtomäki A, Suchting S, Wirzenius M, Waltari M, Hellström M, Schomber T, Peltonen R. 2008. Blocking VEGFR-3 suppresses angiogenic sprouting and vascular network formation. Nature.454:656-660.
Tan C, Zhang L, Cheng X, Lin XF, Lu RR, Bao JD, Yu HX. 2015. Curcumin inhibits hypoxia-induced migration in K1 papillary thyroid cancer cells. Experimental biology and medicine. Jul;240:925-935.
Teymouri M, Pirro M, Johnston TP, Sahebkar A. 2016. Curcumin as a multifaceted compound against human papilloma virus infection and cervical cancers: A review of chemistry, cellular, molecular, and preclinical features. BioFactors. Nov 29.
Thulasiraman P, McAndrews DJ, Mohiudddin IQ. 2014. Curcumin restores sensitivity to retinoic acid in triple negative breast cancer cells. BMC cancer.14:1.
Visioli F, Davalos A. 2011. Polyphenols and cardiovascular disease: a critical summary of the evidence. Mini reviews in medicinal chemistry.11:1186-1190.
Wolff JE, Brown RE, Buryanek J, Pfister S, Vats TS, Rytting ME. 2012. Preliminary experience with personalized and targeted therapy for pediatric brain tumors. Pediatric blood & cancer.59:27-33.
Woo JM, Shin DY, Lee SJ, Joe Y, Zheng M, Yim JH, Callaway Z, Chung HT. 2012. Curcumin protects retinal pigment epithelial cells against oxidative stress via induction of heme oxygenase-1 expression and reduction of reactive oxygen. Molecular vision.18:901-908.
Wright JS. 2002. Predicting the antioxidant activity of curcumin and curcuminoids. Journal of Molecular Structure: THEOCHEM.591:207-217.
Xia Y-P, Li B, Hylton D, Detmar M, Yancopoulos GD, Rudge JS. 2003. Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. Blood.102:161-168.
Xie P, Zhang W, Yuan S, Chen Z, Yang Q, Yuan D, Wang F, Liu Q. 2012. Suppression of experimental choroidal neovascularization by curcumin in mice. PloS one.7:e53329.

Yan H-X, Wang Y, Yang X-N, Fu L-X, Tang D-M. 2013. A new selective vascular endothelial growth factor receptor 2 inhibitor ablates disease in a mouse model of psoriasis. Molecular medicine reports.8:434-438.
Yang K-Y, Lin L-C, Tseng T-Y, Wang S-C, Tsai T-H. 2007. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC–MS/MS. Journal of chromatography B.853:183-189.
Yao Q, Lin Y, Li X, Shen X, Wang J, Tu C. 2013. Curcumin ameliorates intrahepatic angiogenesis and capillarization of the sinusoids in carbon tetrachloride-induced rat liver fibrosis. Toxicology letters. Sep 12;222:72-82.
Yoshida S, Ono M, Shono T, Izumi H, Ishibashi T, Suzuki H, Kuwano M. 1997. Involvement of interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor in tumor necrosis factor alpha-dependent angiogenesis. Molecular and cellular biology.17:4015-4023.
Young BC, Levine RJ, Karumanchi SA. 2010. Pathogenesis of preeclampsia. Annual Review of Pathological Mechanical Disease.5:173-192.
Zabihi NA, Pirro M, Johnston TP, Sahebkar A. 2016. Is there a role for curcumin supplementation in the treatment of non-alcoholic fatty liver disease? The data suggest yes. Current pharmaceutical design. Oct 10.
Zhan Y, Chen Y, Liu R, Zhang H, Zhang Y. 2014. Potentiation of paclitaxel activity by curcumin in human breast cancer cell by modulating apoptosis and inhibiting EGFR signaling. Archives of pharmacal research.37:1086-1095.
Zhang F, Zhang Z, Chen L, Kong D, Zhang X, Lu C, Lu Y, Zheng S. 2014. Curcumin attenuates angiogenesis in liver fibrosis and inhibits angiogenic properties of hepatic stellate cells. Journal of cellular and molecular medicine.18:1392-1406.
Zhang Z-J, Zhao L-X, Cao D-L, Zhang X, Gao Y-J, Xia C. 2012. Curcumin inhibits LPS-induced CCL2 expression via JNK pathway in C6 rat astrocytoma cells. Cellular and molecular neurobiology.32:1003-1010.
Zhao LX, Jiang BC, Wu XB, Cao DL, Gao YJ. 2014. Ligustilide attenuates inflammatory pain via inhibition of NFκB-mediated chemokines production in spinal astrocytes. European Journal of Neuroscience.39:1391-1402.
Zhao W, Wang Y, Wang Y, Gao N, Han Z, Yu H. 2015. Potential anti-cancer effect of curcumin in human lung squamous cell carcinoma. Thoracic Cancer.6:508-516.
Zhong Y, Liu T, Guo Z. 2012. Curcumin inhibits ox-LDL-induced MCP-1 expression by suppressing the p38MAPK and NF-κB pathways in rat vascular smooth muscle cells. Inflammation Research.61:61-67.
Zhu W, Wu Y, Meng YF, Wang JY, Xu M, Tao JJ, Lu J. 2015. Effect of curcumin on aging retinal pigment epithelial cells. Drug design, development and therapy.9:5337-5344.

Table 1. Function and structure features of vascular endothelial growth factor family members/subtypes and receptors.

VEGF family members/subtypes	Function	Structure
VEGF-A	•promotes monocyte activation and chemotaxis(Clauss, Gerlach, Gerlach, Brett, Wang, Familletti, Pan, Olander, Connolly and Stern 1990)(Clauss, Gerlach, Gerlach, Brett, Wang, Familletti, Pan, Olander, Connolly and Stern 1990)(Clauss, Gerlach, Gerlach, Brett, Wang, Familletti, Pan, Olander, Connolly and Stern 1990)(Clauss, Gerlach, Gerlach, Brett, Wang, Familletti, Pan, Olander, Connolly and Stern 1990)	All VEGFs are antiparallel, cystine-knot polypeptide dimers that are covalently linked by two intermolecular disulfide bonds.
	•regulates endothelial cell differentiation	In VEGF-C and VEGF-D, this VEGF homology domain is flanked by C- and N-terminal propeptides that are sequentially cleaved, giving rise to VEGF homologs with distinct functions.
		VEGF-C and VEGF-D exist predominantly as noncovalently linked homodimers, although they both have the conserved cysteine residues that form the interchain disulfide bridges in the other VEGFs.
	•increases vessel permeability	
VEGF-B	•affects cardiac muscle function	Both have also an additional cysteine residue close to the interchain disulfide residues at the dimer interface.
	•has a minor role in angiogenesis regulation	All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface,

		causing them to dimerize and become activated through transphosphorylation, although to different sites, times, and extents.
VEGF-C	•regulates lymphangiogenesis •involved in angiogenesis at the early stage of embryogenesis and in tumor angiogenesis	
VEGF-D	•regulates lymphangiogenesis •involved in angiogenesis at the early stage of embryogenesis and in tumor angiogenesis	
VEGF-E (Orf virus-encoded protein)	•induces epidermal changes such as increase in the number of keratinocyte, endothelial cells and blood vessels within the dermis, as well as induction of epidermal thickening	
PlGF	•affects cardiac muscle function •has a minor role in angiogenesis regulation	
VEFGR		
VEGFR-1 (VEGF-A, VEGF-B and PIGF bind to this receptor)	•has a negative regulation of VEGFR-2 biology and determines the migration of monocytes	VEGFRs have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region and an intracellular portion containing a split tyrosine-kinase domain.
VEGFR-2 (VEGF-A, VEGF-C and VEGF-D bind to this receptor)	•plays essential roles in vascular endothelial progenitors differentiation, vascular permeability, sprouting angiogenesis and endothelial migration, proliferation and survival	The extracellular parts of VEGFR-2 and VEGFR-3 share the same overall structure of 7 immunoglobulin-like domains.
VEGFR-3 (VEGF-C and VEGF-D bind to this receptor)	•induces the migration of lympho-endothelial precursors, lymphatic vessel expansion and blood vascular sprouting angiogenesis	In contrast to VEGFR-1 and VEGFR-2, VEGFR-3 ligand (VEGF-C) binding is D1 dependent

VEGF: vascular endothelial growth factor; PIGF: placental growth factor; VEGFR: vascular endothelial growth factor receptor

Table 2: In vitro studies evaluating the effects of curcumin on VEGF levels.

Reference	Cancer Type	VEGF Type	Curcumin dose	Model	Route of administration	Duration	Findings
In vitro studies							
(Mohankumar, Sridharan, Pajaniradje, Singh, Ronsard, Banerjea, Somasundaram, Coumar, Periyasamy and Rajagopalan 2015)	breast	VEGF	15 µM	MCF-7 cells	-	24h	mRNA expression of VEGF decreased by curcumin.
(Carvalho Ferreira, S Arbab, Victorasso Jardim-Perassi, Ferraz Borin, RS Varma, Iskander, Shankar, M Ali and Aparecida Pires de Campos Zuccari 2015)	breast	VEGF-C	In vitro: 25, 50 and 100 µM	In vitro: MDA-MB-231	-In vitro: -	In vitro: 4 hours and 24 hours	In vitro: There was a dose dependently inhibitory effect of curcumin on the proliferation of breast cancer cells.
			In vivo: 300 mg/kg/day of curcumin administered	In vivo: female athymic mice	In vivo: intraperitoneally	In vivo: 21 days	In vivo: The expression of VEGFR2/3 significantly is reduced in curcumin treated tumors.
(Farhangi, Alizadeh, Khodayari, Khodayari, Dehghan, Khori, Heidarzadeh, Khaniki,	breast	VEGF	In vitro:5, 10, 15 and 20 µM	In vitro: the metastatic breast cancer cell line (4T1)	In vitro: -	In vitro: 24h	In vitro: Both doses of dendrosomal curcumin were safe and decreased the migration and the adhesion

Sadeghiezadeh and Najafi 2015)							of the 4T1 cells in a dose dependent-manner.
			In vivo: 40 and 80mg/kg	In vivo: BALB/c femalemice	In vivo: intraperitoneally	In vivo: 7 days	In vivo:Curcumin suppressed NF-κB expression and its regulated gene products such as VEGF, COX-2, and MMP-9 expressions in the breast tumor, the lung, the brain, the spleen and the liver tissues.
(Thulasiraman, McAndrews and Mohiudddin 2014)	breast	VEGF-A	30 μM	triple negative breast cancer cell line (MDA-MB-231 cells)	-	24 hours	Curcumin and all-trans-retinoic acid reduce VEGF-A expression in MDA-MB-231 cells.
(Anand, Sung, Kunnumakkara, Rajasekharan and Aggarwal 2011)	breast	VEGF	10, 25, 50 μM	MDA-MB-231 (breast adenocarcinoma)	-	4 hours	The results showed that curcumin can downregulate the expression of VEGF.
(Carroll, Benakanakere, Besch-Williford, Ellersieck and Hyder 2009)	breast	VEGF	200 mg kg-1 day-1	female Sprague-Dawley rats	-	26 to 50 days	Curcumin reducedby 34% VEGF induction in hyperplastic lesions.
(Chakraborty, Jain, Kale, Raja, Kumar, Mishra and Kundu 2008)	breast	VEGF	10-50 μM	The human breast adenocarcinoma cell line MDA-MB-231	-	2 h	Curcumin can supress OPN-induced VEGF expression and tumor angiogenesis.
(Carroll, Ellersieck and	breast	VEGF	10 KM μM	T47-D human	-	18 h	Curcumin can

Hyder 2008)				breast cancer cells			reduce medroxyprogesterone acetate (MPA) - induced secretion of VEGF from T47-D cells.

Table 3: In vivo and clinical studies evaluating the effects of curcumin on VEGF levels.

Reference	Disorder	VEGF Type	Curcumin dose	Model	Route of administration	Duration	Findings
Clinical Trials							
(Ganjali, Sahebkar, Mahdipour, Jamialahmadi, Torabi, Akhlaghi, Ferns, Parizadeh and Ghayour-Mobarhan 2014b)	obesity	VEGF	1 gr/day	obese individuals	Oral	4 weeks	Serum VEGF level is significantly reduced by curcumin therapy.
(Wolff, Brown, Buryanek, Pfister, Vats and Rytting 2012)	pediatric brain tumors	VEGF-A	150 mg/kg PO daily	pediatric patients	Oral	a 6-week induction phase, a response evaluation, a 30-week consolidation phase, and 1 year of maintenance treatment	Curcumin can interfere with NF-kB and suppress mTOR as well as modify cell cycle regulation. VEGF level is not improved by curcumin supplement.
(Bayet-Robert, Kwiatowski, Leheurteur, Gachon, Planchat, Abrial, Mouret-Reynier, Durando, Barthomeuf and Chollet 2010)	breast cancer	VEGF	500 mg/d	postmenopausal women or men ≥18 years with breast cancer	Oral	7 consecutive day at each cycle from d-4 to d+2for six cycles	In the eight patients with measurable lesions, VEGF significantly decreased by 30% between baseline andcycle no. 3.

Table 4: Studies evaluating the effects of curcumin on VEGF levels in retinal disorders.

Reference	Disorder	VEGF Type	Curcumin dose	Model	Route of administration	Duration	Findings
In vitro studies							
(Chang, Chang, Hung, Yang, Cheng, Liao, Woung, Tsai, Hsu and Lin 2014)	Age-related macular degeneration (AMD)	VEGF	10 μM	retinal pigment epithelial (RPE) cells	-	24 h	Curcumin modulated the expression of VEGF as an oxidative stress-regulating gene.
(Hollborn, Chen, Wiedemann, Reichenbach, Bringmann and Kohen 2013)	blinding retinal diseases	VEGF-A	10 and 50 μM	human retinal pigment epithelial (RPE) cells	-	6 h	Curcumin inhibits expression and secretion of VEGF-A in a dose dependent manner.
(Xie, Zhang, Yuan, Chen, Yang, Yuan, Wang and Liu 2012)	AMD	VEGF	30 mg/kg	C57BL/6N mice	intraperitoneal	3 days	The results showed curcumin supplementation can suppress RPE–choroid protein levels of VEGF, thereby it can improve age-related macular degeneration (AMD)-associated CNV.
(Li, Wang, Ying, Chen and Yu 2016)	Diabetic retinopathy	VEGF	30 mg/kg	Rat model of diabetic retinopathy	oral gavage	12 weeks	The administration of curcumin can downregulate the VEGF in rat model of diabetes.

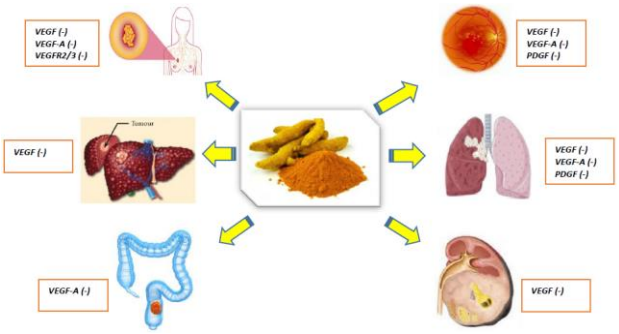

Figure 1. Effects of curcumin on vascular endothelial growth factor (VEGF) and VEGF-VEGF receptor (VEFGR) 2 signaling pathway. PDGF: platelet derived growth factor.