Pharmacological Research 137 (2018) 159–169

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Effects of curcumin on hypoxia-inducible factor as a new therapeutic target

Afsane Bahrami[a], Stephen L. Atkin[b], Muhammed Majeed[c], Amirhossein Sahebkar[d,e,f,*]

[a] Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran
[b] Weill Cornell Medicine Qatar, Doha, Qatar
[c] Sabinsa Corporation, East Windsor, NJ, USA
[d] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[f] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Keywords:
Aryl hydrocarbon receptor nuclear translocator
Hypoxia-responsive elements
Turmeric
Von Hippel-Lindau

ABSTRACT

Hypoxia-inducible factor-1 (HIF-1) is a transcription factor that consists of two subunits, the HIF-1α and HIF-1β (ARNT). Under hypoxic conditions, HIF-1 is an adaptive system that regulates the transcription of multiple genes associated with growth, angiogenesis, proliferation, glucose transport, metabolism, pH regulation and cell death. However, aberrant HIF-1 activation contributes to the pathophysiology of several human diseases such as cancer, ischemic cardiovascular disorders, and pulmonary and kidney diseases. A growing body of evidence indicates that curcumin, a natural bioactive compound of turmeric root, significantly targets both HIF-1 subunits, but is more potent against HIF-1α. In this review, we have summarized the knowledge about the pharmacological effects of curcumin on HIF-1 and the related molecular mechanisms that may be effective candidates for the development of multi-targeted therapy for several human diseases.

1. Introduction

Hypoxia is defined as lack of oxygen in cells, tissues or in organs. Hypoxic conditions can develop due to a diminished supply of oxygen through anemia, or a defective blood vessel network or due to excessive consumption relative to supply as seen in the high proliferative rate found in cancer [1]. It is a non-sustainable cellular condition in which low oxygen pressure hinders the normal function of cell [2]. Adaptation to hypoxia occurs as a homeostatic mechanism in all the cells. In the absence of oxygen, cells recruit different adaptive mechanisms for growth and survival under hypoxic stress by regulating the expression of genes responsible for glucose uptake, transport, and metabolism, erythropoiesis, inflammation, angiogenesis, cell proliferation, pH regulation, and cell death [3]. The cellular response to acute hypoxia is triggered by the up regulation of hypoxia inducible factors (HIF), which are a family of evolutionarily conserved transcriptional factors (TF) that influence the physiological response to low oxygen [4]. HIF-1, is one important member of the HIF family that is composed of two subunits, the stable beta (HIF-1β) and the labile alpha (HIF-1α) [5]. Under normoxic conditions, HIF-1α is hydroxylated by prolylhydroxylase domain proteins, and is rapidly degraded through the ubiquitin-proteasomal degradation pathway. Under a hypoxic state, the HIF-1α subunit is not hydroxylated and thus forms a stable complex with HIF-1β. The active HIF-1 translocates into the nucleus and binds to 5′-RCGTG-3′ core sequences in hypoxia-responsive elements (HRE) located on the promoter region of hypoxia sensitive genes [6,7].

Cellular HIF-1 activation stimulates glucose utilization for the generation of ATP to maintain cell proliferation and survival under stress conditions such as nutrient deficiency and cell damage [8]. HIF-1 activation results in modulation of the cell cycle and may result in cell cycle arrest during hypoxia [9], protecting against hypoxia induced cell damage [10]. Cellular and systemic stresses are regulated by a combination of short- and long-term response pathways acting through the activity and transcription of a plethora of cellular proteins. At the cellular level, a molecular response is initiated in which gene expression is altered to assist the cells to adapt to the stressful environment. For example, HIF-1-dependent mRNA transcription of erythropoietin and angiogenic factors leads to elevated neoangiogenesis to facilitate the increased supply of oxygenated blood to the hypoxic tissue. In addition, HIF-1 stimulates the glycolytic enzymes leading to the generation of energy when the mitochondria are starved of oxygen impairing the electron transport chain [11]. Furthermore, HIF-1 not only mediates the delivery of oxygen from the peripheral blood, but also helps modulate oxygen demand through decreasing the action of mitochondria, the

* Corresponding author at: Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, P.O. Box: 91779-48564, Iran.
E-mail addresses: sahebkara@mums.ac.ir, amir_saheb2000@yahoo.com (A. Sahebkar).

https://doi.org/10.1016/j.phrs.2018.10.009
Received 1 October 2018; Received in revised form 7 October 2018; Accepted 9 October 2018
Available online 10 October 2018

main cellular consumer of O_2. Depending on the severity and length of the hypoxic stimulus, HIF-1 induces the expression of genes that can be adaptive (e.g. inducible nitric oxide synthase) or deleterious (e.g. endothelin-1) responses [11]. For instance, the response of proto-oncogene c-jun mRNA expression and phosphorylation against extended or chronic hypoxia is dependent on the existence of HIF-1 [12]. Under chronic exposure to hypoxia, HIF-1α levels may be amplified to address the balance between oxygen supply and tissue demand. While hypoxia is a major stimulant for HIF-1 expression, HIF-1 can also be stimulated by other types of stress, such as the over-expression of HIF-1α levels after endoplasmic reticulum (ER) stress [13] following chemical hypoxic neuronal death [14].

Transcriptional activation by HIF1 induces the expression of genes that mediate the metabolic regulation of the hypoxic cell, induces angiogenesis around the hypoxic tissue, and promotes cell survival. Thus, HIFs are essential for embryonic development, but are also exploited by cancer cells during tumor progression [15,16]. Increasing evidence has shown that HIF-1 contributes to tumor initiation and development by modulating the expression of hypoxia-inducible genes and stabilization of the HIF-1α transcription complex promotes tumor progression and metastasis [17–19]. It has been shown that an increased level of HIF-1α was closely related to the aggressive behavior of tumors and poorer patient outcomes [6,20]. In recent years, inhibiting HIF1 has emerged as a new target for cancer therapy. Consequently HIF1 has been targeted at the level of transcription, post-transcription, translation, post-translational modification, ubiquitin/proteasome-protein degradation, DNA binding, and regulation of target genes [21–23]. Several reports have indicated that curcumin, a natural bioactive compound of turmeric root, significantly targets both HIF-1 subunit levels, but is more potent against HIF-1α. In this review, we summarize the finding of the preclinical studies reporting the pharmacological effects of curcumin on HIF-1 and the related molecular mechanisms, which may be effective candidates for the design of a multi-targeted therapy for different human diseases.

2. HIF structure

HIFs is a heterodimer protein comprising of two distinct subunits, HIF-α and HIF-β (also known as ARNT; aryl hydrocarbon receptor nuclear translocator) [24].These two subunits belong to the basic helix loop helix (bHLH) proteins of family of TFs named PER-ARNT-single-minded protein (PAS) [25]. Until now, three HIF-α subunits (HIF-1α, HIF-2α, and HIF-3α) and two HIF-β subunits (HIF-1β (or ARNT) and ARNT2) have been identified [26]. Three HIF-1α mRNAs are transcribed from human *HIF1A* gene, while only one HIF-2α mRNA is coded from the human endothelial PAS domain protein 1 (*EPAS1*; alternatively named *MOP2*) gene (Fig. 1). Both HIF-1α and HIF-1β are members of the family of the bHLH and PER-ARNT-SIM (PAS) domain-containing transcription factors and are constitutively expressed, but HIF-1α is oxygen-sensitive and is degraded via the proteasome pathway [24]. HIF-1β is stable protein and is also an obligate partner for the aryl hydrocarbon receptor (AHR) [27]. HIF-1α and HIF-2α can bind to the HIF-1β subunit and are critical for hypoxia response, while the role of HIF-3α is not very clear. HIF-2α has a similar structure to HIF-1α, and they share the domains that are important for DNA binding and dimerization, a central oxygen-dependent degradation domain (ODD), two transactivation domains and the N and C terminal activation domains (NTAD and CTAD) [28]. The N-terminal transactivation domains of HIF-1α and HIF-2α are essential for targeting gene specificity, while the CAD contributes to the regulation of most, but not all, HIF target genes [29]. HIF-1α is widely expressed in all tissues, but HIF-2α is expressed only in certain tissues [30]. HIF-1β is commonly expressed; however, ARNT2 expression is limited to the kidney and brain of rats and mice [31,32].

During low O2 (hypoxic) conditions, the CTAD of HIF-1α (amino acids 786–826) contributes to regulating the transcriptional activation

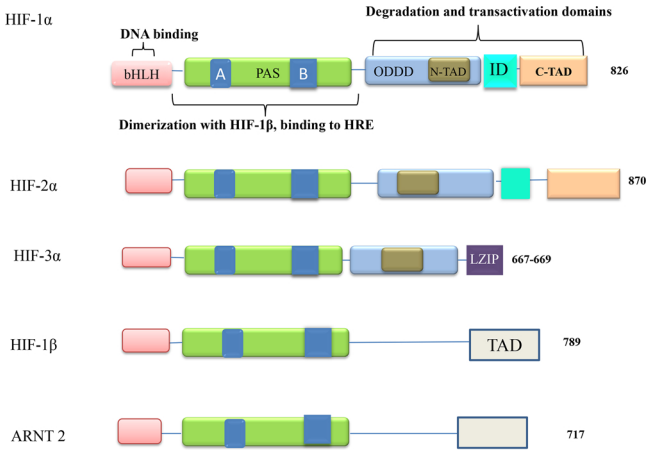

Fig. 1. Hypoxia-Inducible Factor-1 (HIF-1) structures. ARNT; Aryl hydrocarbon receptor nuclear translocator, bHLH: basic helix-loop-helix, C-TAD: C-terminal transcriptional activation domain, LZIP: leucine zipperdomain, N-TAD: N-terminal transcriptional activation domain, ODDD: oxygen-dependent degradation domain, PAS: Per-Arnt-single-minded protein (Sim), TAD: transcriptional activation domain.

of HIF-1α, while the NTAD (amino acids 531–575), contributes to the stability of HIF-1α. In response to hypoxia, the CTAD binds with transcriptional co-activators, such as steroid receptor coactivator-1 (SRC-1), redox factor-1 (Ref-1) and in particular with p300/cAMP-response element-binding protein (CBP) [33]. The interaction between HIF-1α and p300/CBP does not occur in normoxia because hydroxylation of CTAD via an asparaginyl hydroxylase (also known factor inhibiting HIF-1; FIH-1) is O_2-dependent [34]. CTAD hydroxylation restricts HIF-1α from binding to p300/CBP and impairs HIF transcriptional activity; therefore, targeting the complex of HIF-1α, p300/CBP and DNA binding has the potential to be a novel approach for the direct blocking of HIF-1 action.

HIF-3α has 55% identity with HIF-1α and HIF-2α in the two bHLH and PAS domains, but lacks the CTAD and so is unable to interact with p300/CBP [35]. In humans and mice, HIF-3α dimerizes with HIF-β, and this complex induces the transcription of HRE reporter genes in the genome. The amplification and mechanism of action related to HIF-3α is not fully understood [36].The inhibitory PAS domain protein (IPAS) is an alternative splicing variant of the HIF-3α locus that can interact with HIF-1*α* and negatively regulates HIFα [37].

3. HIF-1α regulation

Under normoxia, HIF-1α has a short life and is rapidly degraded through series of events. In humans, HIF-1α protein undergoes hydroxylation of proline (P) residues (402 and 564 for HIF-1α, 405 and 531 for HIF-2α, 406 and 492 for HIF-3α) [38]catalyzed by a unique enzyme, HIF-prolyl hydroxylases (PHD). This enzyme needs iron, α-ketoglutarate, ascorbate and O_2 [38]. The hydroxylated protein is captured by the von Hippel-Lindau (VHL) tumor suppressor protein, which recalls the class of Cullin-2/Elongin-B/C ubiquitin complex (CBC) E3 ligase. The HIF-1α-pVHL binding as part of the ECV complex (Elongin/Culin/VHL) progresses through acetylation of HIF-1α at an internal lysine (K) residue 532 via an acetyltransferase ARD1 [39]. This interaction rapidly results in polyubiquitylation and degradation through the 26S proteasome. Under hypoxic tension, the PHDs are impaired and HIF-1α is not hydroxylated inhibiting the binding with pVHL and degradation. Therefore, HIF-1α accumulates and translocates into the nucleus where it dimerizes with HIF-1β [40]. This active heterodimer directly binds to the HRE (5′-A/GCGTG-3′) in the promoter region to triggers transcription of nearly 40 genes, whose proteins have a broad and complex role in the adaptive pathway for continuing growth and

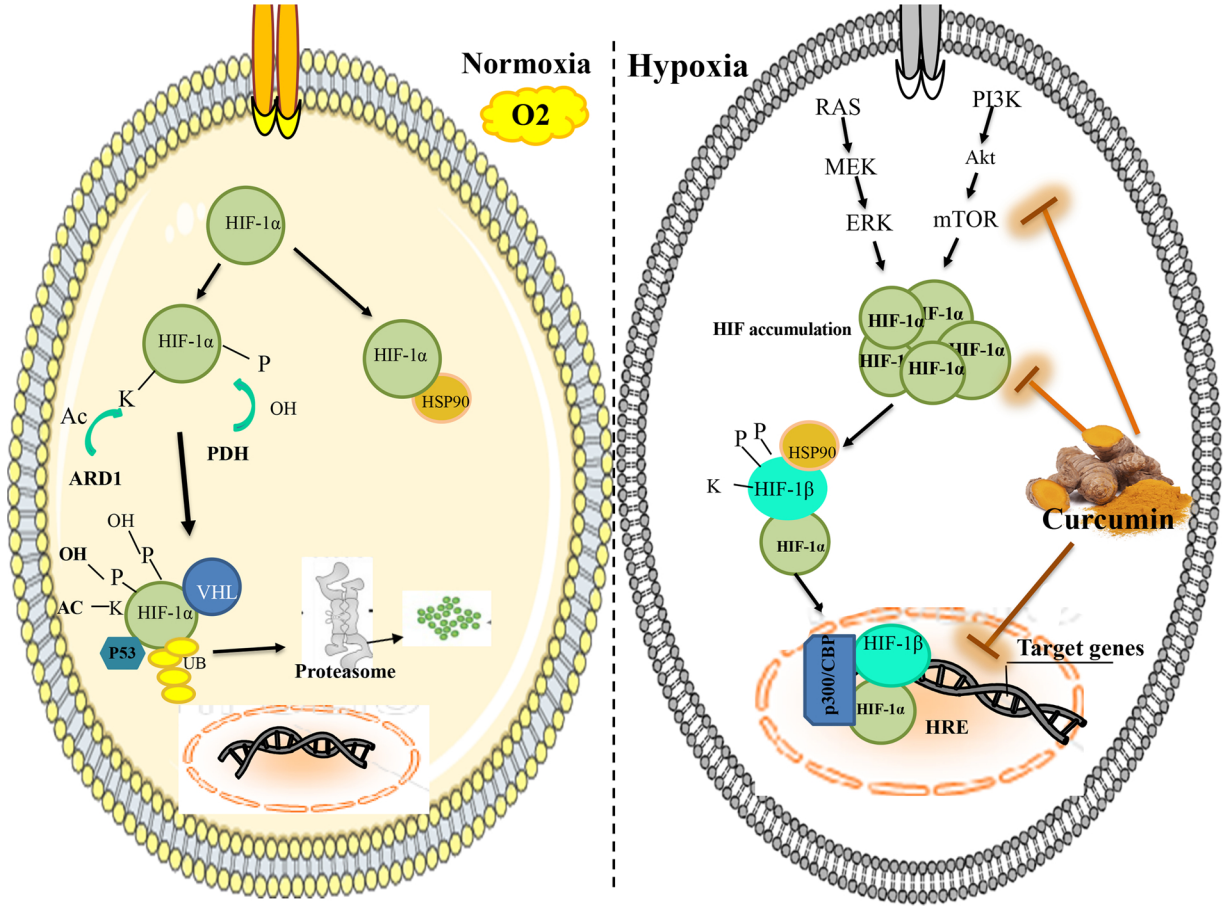

Fig. 2. Overview of cellular HIF-1α pathway in both normoxic and hypoxic conditions and curcumin effects. Under normoxia, HIF-1α is rapidly degraded through hydroxylation of proline residues by a HIF-prolyl hydroxylases (PHD). The hydroxylated protein is captured by the von Hippel-Lindau (VHL) protein and subsequent acetylation of HIF-1α at lysine via an acetyltransferase ARD1. This interaction leads to rapid polyubiquitylation and degradation through the proteasome. Under hypoxic tension, the PHDs are impaired and HIF-1α is not hydroxylated inhibiting the binding with pVHL and degradation. Therefore, HIF-1α accumulates and translocates into nucleus and dimerizes with HIF-1β. This active heterodimer directly binds to the in the promoter region to trigger transcription of target genes. Curcumin decreasesHIF-1α and inhibits the transcription of genes-induced by HIF. ARD1: CBP:cAMP-response element-binding protein, HRE: hypoxia-responsive elements, HSP: Heat shock proteins, mTOR: mammalian target of rapamycin, PDH: prolyl-4-hydroxylase, PI3K: phosphatidylinositol-3-kinase, UB: ubiquitylation, VHL: Von Hippel-Lindau.

metabolism under hypoxic conditions [23].

An additional pathway for HIF-1α degradation/stability is attributed to ATPase-directed chaperone heat shock protein 90 (Hsp90) (Fig. 2). Hsp90 binds directly with HIF-1α causing conformational changes in HIF-1α that result in the formation of HIF-1α/ARNT heterodimers [41]. Hsp90 inhibitors such as galdanamycin (GA) break down the association between HIF-1α and Hsp90, hindering HIF-1α transcriptional activity and also increase the ubiquitination-proteasome degradation of HIF-1α independent of O_2 and VHL protein [42]. Proline mutations of HIF-1α at position 402 and 564 cannot prevent GA-induced HIF-1α degradation, indicating that Hsp90 recruits a new E3 ubiquitin ligase.

The imbalance between the production and destruction of cellular HIF-1α is stringently balanced under normal situations; however, accumulation of HIF-1α occurs when either its production is increased or its degradation is decreased. Alongside the stability of HIF-1 under intra tumoural hypoxia, HIF-1 hyper-activation and decreased degradation may also be observed in normoxic situations (Fig. 2). This event likely happens due to the activation of a series of potent growth-stimulating factors [e.g. growth factors, cytokines] or oncogenic signaling cascades [e.g. NF-κB, mitogen-activated protein kinase (MAPK)]. These growth-stimulating elements potentially activate HIF-1, inducing HIF-1α translation as well as causing downstream signaling transduction pathway activation that may lead to malignancy [43].

Among different oncogenic pathways, alterations in phosphatidylinositol-3-kinase(PI3K)/Akt/mammalian target of rapamycin (mTOR) have a marked impact on HIF-1α protein activation [44]. Changes in the PI3K cascade are frequently involved in cancer formation through different mechanisms including constitutive activation of receptor tyrosine kinases (RTKs) causing to PI3K activation; loss of the tumor suppressor, phosphatase and tensin homologue (PTEN) function; PI3K mutations and dysregulation of AKT [45,46]. Indeed, the mTOR enhances HIF-1α protein translation through phosphorylation of the eukaryotic initiation factor 4E (eIF4E), which binds to mRNA 5′ cap under normoxic states. Although, there are several conflicting reports on the PI3K/Akt/mTOR axis effects on HIF-1α levels in various cell lines [47].

The MAPK signaling also contributes to the expression and activity of HIF-1α [48,49]. It has been shown that activation of the Ras/MAPK module increases the protein production of HIF-1α that interacts with eIF4E [50]. Higher-expression of the ERK1/2 (alternatively called p44/42) as down-stream molecules of Ras/Raf/MEK-1/ERK1/2 pathway, may also significantly promote HIF-1 function [51]. These studies also showed that MAPK pathway could transactivate HIF-1α by phosphorylation [52]. Repression of MAPK phosphorylation accelerated HIF-1α ubiquitin-degradation and hindered HIF-1α translocation to the nucleus.

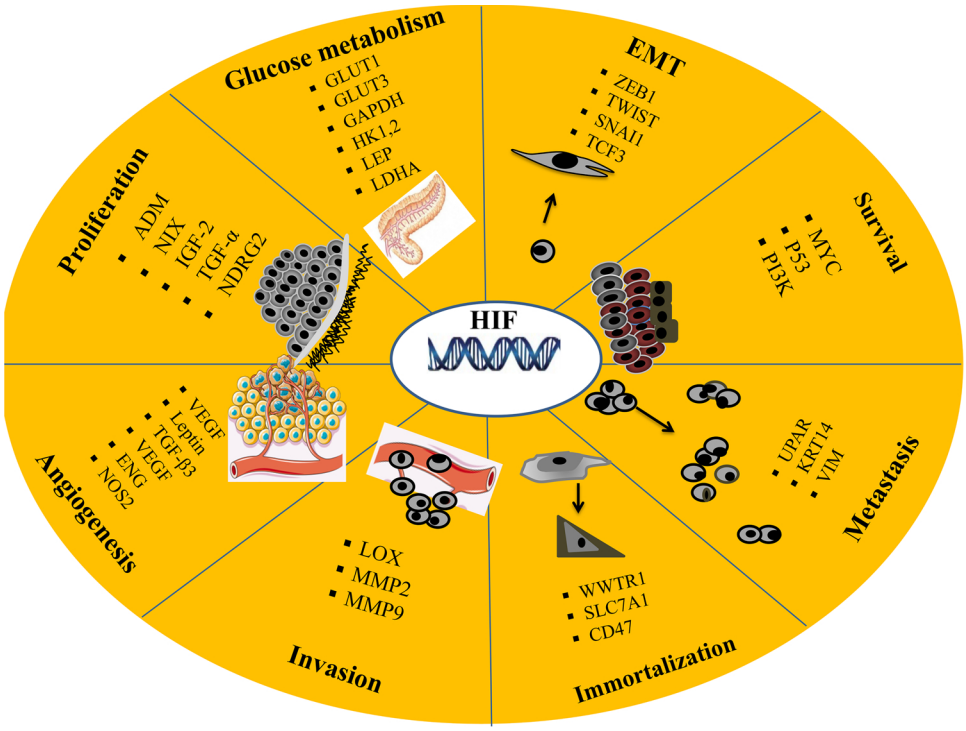

Fig. 3. HIF and its target genes. ADM: Adrenomedullin, ENG: Endoglin, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, GLUT: Glucose transporter, HK: hexokinase, IGF-2: Insulin-like growth factor 2, KRT14:keratin 14, LDH A: Lactate dehydrogenase A, LOX:lysyl oxidase, MMPs: Matrix metalloproteinases, NDRG: N-myc downstream regulated gene, NOS2: Nitric oxide synthase2, PI3K: phosphatidylinositol-3-kinase,SLC7A1: solute carrier family 2 member 1, SNAI1: snail family transcriptional repressor 1, TGF: Transforming growth factor, TCF3:transcription factor 3,VEGF: vascular endothelial growth factor,UPAR: urokinase plasminogen-activator receptor, VIM:vimentin,WWTR1: WW domain containing transcription regulator 1, ZEB1: zinc finger E-box binding homeobox1.

4. HIF-1 target genes

Hundreds of target genes are reported to be affected via HIF in different cell types, in which their protein products regulate erythropoiesis, angiogenesis, metabolism, pH regulation, stem cell maintenance, inflammation, autophagy, cell proliferation and survival, glucose metabolism, immunity, cell invasion and metastasis [53]. Thus, HIF-1, HIF-2 and HIF-3 are actively involved in the pathophysiology of several human diseases such as benign and malignant neoplasms, ischemic cardiovascular disorders, pulmonary and kidney disease [53]. Activation of HIF-1 leads to the over-expression of more than 100 potential target genes that are integrally involved in tumor metastasis, angiogenesis, energy metabolism, cell differentiation and apoptosis [54] (Fig. 3).

5. HIF-1 and cancer

5.1. Tumor angiogenesis

Vascular differentiation is an important aspect tumor pathology and progression. HIF1 stimulates angiogenic response by inducing the expression of vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS), stromal cell-derived factor 1 (SDF1) and adrenomedullin (ADM)], stem cell factor (SCF) and angiopoietin 2 (ANGPT2) [55,56]. Calcitonin receptor-like receptor (CRLR), a G protein receptor promoting angiogenesis and Semaphorin 4D (Sema4D), a member of semaphorins, which promotes angiogenesis are regulated by HIF-1 activity [57,58].

5.2. Metastasis

Tumor metastasis is a critical step in its progression. The transcription factor TWIST which mediates epithelial-mesenchymal transition (EMT) and cancer metastasis is directly regulated by HIF-1 [59]. Apart from this, HIF-1 also regulates the expression of matric metalloproteases, E cadhedrins and adhesion molecules [60,61].

5.3. Glucose metabolism

A shift in glucose metabolism from mitochondrial oxidative to anaerobic glycolysis is seen in cancer cells. Hexokinase (HK) 1, HK2, glucose transporter (GLUT)1, GLUT3, solute carrier family 2 member 1(SLC2A1), glyceraldehyde-3-P-dehydrogenase(GAPDH), pyruvate kinase M(PKM) and lactate dehydrogenase A (LDHA) have been shown to be regulated by HIF-1 [62]. Two glycolytic enzymes, namely phosphoglycerate kinase 1 (PGK 1) and pyruvate kinase M2 (PKM2) monocarboxylate transporter MCT4 and pyruvate dehydrogenase kinase 1 (PDK1) are also transactivated by HIF-1 resulting in a shift in energy metabolism in cancer cells [63,64].

5.4. Cell proliferation and survival

Hypoxic culture appears to be necessary to maintain full pluripotency of human embryonic stem (hES) cells. Erythropoietin (EPO), insulin-like factor-2 (IGF2), transforming growth factor-α (TGF-α), plasminogen activator inhibitor-1 (PAI-1), connective tissue growth factor (CTGF) and platelet derived growth factor (PDGF)], are controlled by HIF-1

6. HIF-1 and fibrosis

Fibrosis, characterized by increased extracellular matrix (ECM) deposition, and widespread vasculopathy is associated with chronic hypoxia [65]. HIF-1α is implicated in producing excessive ECM, which is the underlying cause of fibrosis [66]. High levels of expression of HIF-1α was found in fibrotic dermal fibroblasts cultured under hypoxic conditions. HIF-1α induces collagen hydroxylation and normal collagen secretion in hypoxia by directly activating transcription of the collagen prolyl 4-hydroxylase enzyme (P4H) and pyruvate dehydrogenase kinase 1 (Pdk1) [67].

7. HIF and vascular remodeling

Dysregulated proliferation of endothelial cells (ECs) and an increase in the number and volume of arterial smooth muscle cells (ASMC)

results in progressive vascular occlusion during vascular remodeling. There is a strong correlation between vascular remodeling and hypoxia that has been reported by several studies [68,69]. HIF-1 was found to increase the expression of proteins implicated in vascular remodeling, including transient receptor potential channel (TRPC) 1 [70], Platelet derived growth factor bb (PDGFbb) [71], hepatocyte growth factor (HGF) [72] and stromal-derived factor-1α (SDF-1α) [73], which play a role in proliferation of EC and VSMC.

8. Curcumin

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6- heptadiene-3,5-dione] is an active phenolic pigment extracted from dried rhizomes of turmeric (*Curcuma longa*), which is a herbaceous tropical plant and native to southeast Asian and Middle Eastern countries [74]. Chemically, commercial curcumin consists of nearly 80% diferuloylmethane (curcumin), 17% demethoxycurcumin (DMC), and 3% bisdemethoxycurcumin (BDMC) [75].

Functional groups of curcumin are reactive bis-α, β unsaturated β-diketone, methoxy and phenolic hydroxy groups as well as double-conjugated bonds [76]. Curcumin is a multifunctional molecule possessing a wide range of cellular targets and has been reported to have antioxidant [77–80], anti-prolifrative [81,82], analgesic [83,84], anticoagulative [85], immunomodulatory [86], antidiabetic [87], hepatoprotective [88,89], anti-bacterial [90], lipid-regulating [91–94] and anti-inflammatory properties [95–97]. The multiple functions of curcumin are attributed to the α,β-unsaturated β diketone group, which covalently binds to proteins [98]. Moreover curcumin affects all stages of tumor development including transformation, proliferation and progression [98–100].

Curcumin has significant cytoprotective effects through reducing lipid peroxidation, inflammation and oxidative stress, elevating intracellular antioxidants, scavenging free radicals, and regulating antioxidant or pro oxidant enzymes [101]. This compound exert its cellular functions directly and indirectly through different molecular mechanisms such as regulation of the RAS [102], PI3K/AKT [103], MEKK1-JNK,AMPK, Nrf2–KEAP1 [104],Wnt/β-catenin and TGF-β1/Smad (transforming growth factor-β1/drosophila mothers against decapentaplegic protein) signaling pathways, and modulation of variety of biochemical molecules including TFs, oncogenes and tumor suppressor genes, protein kinases, adhesion molecules, cell surface receptors, growth factors and their receptors, proteases, enzymes, cell cycle regulatory proteins, transcriptional coactivator, transporters, and apoptotic factors [105–107]. Curcumin also shows inhibition of the proinflammatory mediators such as TNF-α, NFκB, toll-like receptor 4 (TLR4) and TLR2, interleukelin-6 (IL-6), and up-regulation of VEGF, all of which are involved in tumor formation [108,109].

Different laboratory studies and clinical trials have shown that curcumin has therapeutic potential in chronic diseases such as cancer, inflammatory, cardiovascular, pulmonary, metabolic and neuropsychological disorders.

9. Effect of curcumin on HIFs in metabolic diseases and liver fibrosis

Several studies have highlighted the role of HIF-1α in obesity and obesity-associated metabolic diseases [110,111]. Dysfunctional adiposity results from visceral fat mass excess, adipokine and inflammatory deregulation, insulin resistance and furthermore, by fibrosis of adipose tissue under hypoxia [112]. HIF-1α modulates the expressions of genes responsible for fibrosis and the inflammatory response, which indicates the involvement of HIF-1α in the genesis and progress of fibrosis and inflammation-associated with adipose tissue dysfunction [113]. Recently Qiu et al reported that curcumin prevented adipose hypoxia by decreasing oxygen use as well as preventing HIF-1α-related adipose fibrosis by the inhibition of the AMPK/mTOR axis [114].

Liver fibrosis results from the accumulation of extracellular matrix after tissue injury in mammalian. Innate and adaptive immune systems, angiogenesis and HIF-1 participate in the formation and development of tissue fibrosis[115]. Following tissue injury, the hepatocytes undergo apoptosis that can lead to a hypoxic environment causing HIF-1 activation. It has been shown that curcumin has a beneficial effect in liver fibrosis by reducing HIF-1α and ERK1/2 expression levels through several mechanisms including: a), blocking cell proliferation; b), suppression of gene expression of collagen III, and α-smooth muscle actin. Curcumin may protect from liver fibrosis induction through suppressing of HIF-1α via the ERK-dependent processes [116].

Recently, the effect of curcumin was assessed on hepatic succinate accumulation and liver fibrosis in mice that had received a high-fat diet. It was observed that hepatic succinate accumulation acts as a metabolic signal for liver fibrosis via HIF-1α induction. Knockdown of HIF-1α by small interfering RNA (siRNA) prevented succinate stimulation of HSCs activation, showing the critical role of HIF-1α in succinate signaling [117]. Oral supplementation of curcumin and metformin prevented hepatic fibrosis through inhibition of mitochondrial fatty acid oxidation, and succinate dehydrogenase activity, as well as decreasing hepatic succinate accumulation. In mouse primary hepatic stellate cells (HSCs) under hypoxia-mimicking conditions (CoCl2 treatment), curcumin impaired succinate-associated HIF-1α induction by reducing ROS generation, inflammation and expression of fibronectin and TGF-β1 [117]. This finding implies that HIF-1α might be a potential target for curcumin in the treatment of liver fibrosis. Curcumin was found to protect the rat liver from CCl_4-caused injury and fibrogenesis by reducing the expression of HIF1 [118].

10. Effect of curcumin on HIFs in diabetes

Both hyperglycaemia and hypoxia are implicated in the adverse diabetic complications such as diabetic retinopathy, nephropathy and neuropathy, late wound healing, as well as cardiovascular disease. Deregulation of HIF-1 is directly related to the lack of cellular adaptation to hypoxia in diabetes with increasing evidence suggesting that high glucose levels destabilize HIF-1α during hypoxia by [119]. Hyperglycemia appears to impair hypoxia-dependent stabilization of HIF-1α through proteasomal degradation. Studies have shown a linear correlation of blood glucose to fatal outcome related post-acute hypoxic tensions such as seen in acute myocardial infarction [120], suggesting that hyperglycemia may impair the tissue's ability to adapt to acute low oxygen conditions.

During wound-stimulated hypoxia, HIF-1α is highly regulated and induces synthesis of VEGF and SDF-1α [121,122], leading to the accumulation of endothelial progenitor cells (EPCs) and promotion of angiogenesis [123]. There is increasing evidence suggesting that curcumin may protect against diabetic complications [124]. Kant *et al* reported that a combination of substance P (SP) and curcumin significantly accelerated wound healing in diabetic rats through increasing the expressions of IL-10, VEGF, TGF-β1, HIF1-α, SDF1-α, heme oxygenase-1 (HO-1) and endothelial NOS, as well promoting activities of superoxide dismutase (SOD) and catalase (CAT) in the granulation tissue. The high expression of HIF-1α, SDF-1α and VEGF in the combination-treatment group favors synthesis of new blood vessels, enhancing the wound healing process [125]. It has also been reported that curcumin treatment significantly contributes to neovasculogenesis and rapid wound closure in diabetic rats by increasing the expression of VEGF, TGF-β1, HIF1-α, SDF-1α and HO-1 compared with controls [126]. However, human clinical studies will be needed to confirm these findings

11. Effect of curcumin on HIFs in cancer

Accumulating evidence suggest that hypoxic signaling is involved in the modulation of the cellular physiology of tumor cells (Table1)

Table 1
Overview of preclinical finding about the effect of curcumin on HIF.

Condition	Type of cell lines or animal model	Dosage; Period of curcumin	Effect	Reference
Liver fibrosis	Sprague-Dawley rats	400 (low dose), 1200 (high dose) mg/kg; 6 weeks	-decreasing HIF-1α and ERK1/2 expression -decrease cell proliferation, suppression of gene -suppression of collagen III, and α-smooth muscle actin	(113)
	Mice fed a high-fat diet	50 mg/kg ; 10 days	-inhibit of mitochondrial fatty acid oxidation, and succinate dehydrogenase activity -inhibit succinate-associated HIF-1α induction	(114)
HCC	HepG2 human hepatoblastoma cells and HEK 293 cells	50 μM; 24 h	-reduced the expression of HIF-1α in vascular endothelial cells - decrease HIF-1α protein levels in HCC cells -down-regulate VEGF	(122)
	Cells from the human hepatoma cell line	10 μmol/l; 12 h	-reduce of HIF-1α-mediated angiogenesis -reduction of hypoxia-induced HIF-1α	(107)
Different cancer	- Cell lines (Hep3B hepatoma, MKN28 gastric carcinoma, MCF7 mammary carcinoma, HT29 colon carcinoma, PC3 prostate carcinoma, Caki-1 renal carcinoma, SiHa cervical carcinoma, and H596 non–small-cell lung carcinoma) -Male nude (BALB/cAnNCrj) mice with xenografted cancers	120 mg/kg; once a day for 5 days	-prevent of HIF-1 activity -inhibit of HIF-1genes regulation -increased proteaosomal degradation of ARNT	(129)
	-Human breast cancer MDA-MB-231 cells - human prostate cancer PC3 cells	curcumin	-suppression of HIF-1α gene transcriptions through VHL-dependent manner	(127)
	- human ovarian carcinoma 1A9cells	EF24	-suppression of HIF-1α post-transcriptionally through VHL-dependent manner -disrupts the microtubule cytoskeleton	
	-Cell lines Hep3B, HepG2 (hepatoma) -MCF-7 (breast adenocarcinoma)	5–100 μM; 4 h or 0–25 μM ; 24 h	-induce HIF-1α and HIF-2α degradation	(133)
Pituitary adenomas	-Corticotroph AtT20 mouse tumor cells -lactosomatotroph GH3 rat pituitary tumor cells -human pituitary adenoma cell cultures	0.5–30 mM; 72 h	-inhibits HIF1-α protein value - down-expression of HIF-1α mRNA	(134)
Prostate cancer	fibroblast-driven prostate cancer (PC3 cells)	25 μM; 72 h	-inhibit CAF-associated aggression and EMT -reduce expression of CXCR4 and IL-6 receptor by ameliorating MAO/mTOR/HIF-1α signaling -inhibited CAF-induced ROS genesis via the MAO/mTOR/HIF-1α axis	(141)
Lung adenocarcinoma	Human lung adenocarcinoma cell lines (A549 cells and the cis-platin resistant A549/DDP cells)	5,10, 15 and 20 μM; 48 h	- down-regulation of HIF-1-dependent P-glycoprotein - decrease HIF-1 protein level - induced apoptosis through enhancing HIF-1α degradation and activating caspase-3	(147)

Abbreviations: ARNT :Aryl Hydrocarbon Receptor Nuclear Translocator, Bcl-2 :B-cell lymphoma 2, CAF-1: CAF-1: cancer-associated fibroblasts, COX-2:cyclooxygenase-2, EMT: epithelial–mesenchymal transition, ERK1/2: extracellular signal-regulated kinase 2, HCC: hepatocellular carcinoma, HIF-1α : hypoxia inducible factor-1α, IL:interleukin,MAO: monoamine oxidase, mTOR: Mammalian target of rapamycin;NF-κB :nuclear factor-kappa B; ROS:reactive oxygen species, TGF-β1: Transforming growth factor beta1,VEGF: vascular endothelial growth factor, VHL: von Hippel Lindau.

[127,128]. Intratumoral hypoxia results in the accumulation of HIF-1α and HIF-2α in tumor and stromal cells. Notably, hypoxia is related to a poor prognosis and elevated levels of HIF-1α protein are associated with a poor outcome and increased mortality rates [129–131]. Curcumin was found to reduce HIF-1 activity in several human tumor cell lines (Table 1).

It has been shown that accumulation of hypoxia-mediated HIF-1α stimulates the expression of β-catenin, increases EMT process, enhances invasiveness and metastatic behavior of hepatocellular carcinoma (HCC) *in vitro* and *in vivo* [132]. Curcumin decreased the expression of HIF-1α in vascular endothelial cells and HIF-1α protein levels in HCC cells, which resulted in down-regulation of VEGF that is a master HIF-1 target angiogenesis factor [133]. This finding demonstrated the crucial role of HIF-1α in EMT alteration, and especially in cancer progression under hypoxic stress. Moreover, curcumin is a potential anticancer agent by inhibition of HIF-1α-mediated angiogenesis [134].

Tetrahydrocurcumin (THC) is the colorless metabolite of turmeric, obtained from hydrogenation of curcumin. Yoysungnoen and colleagues investigated the effects of THC on tumor angiogenesis and mechanisms of action in cervical cancer (CaSki) injected nude mice. Results showed that THC significantly restricted tumor angiogenesis in animal models of cervical cancer by decreasing microvascular density and reducing protein expression levels of HIF-1α, VEGF and VEGFR-2. This finding highlighted the protective role of curcumin against cancer formation through repression of HIF-1α and VEGF/VEGFR-2 pathways [135].

The bromophenol curcumin [1,5-bis(3-bromo-4, 5-dimethoxyphenyl) penta-1, 4-dien-3-one] analogue of curcumin has shown antiangiogenic properties in the treatment of cancer. Bromophenol curcumin induced apoptotic death and suppressed migration, invasion, proliferation and tubular formation in human umbilical vein endothelial cell (HUVEC) via HIF-1α/VEGF/Akt signaling pathways [136].

Because of the low bioavailability and efficacy of cucumin in preclinical studies, several novel analogues of curcumin have been developed [98,137]. EF24, a potential curcumin-related compound analog, showed higher biological activity and bioavailability compared to curcumin. Thomas *et al* reported that both EF24 and curcumin effectively inhibited HIF-1α protein concentrations and transcriptional activity in breast and prostate cancer cell lines. However, curcumin prevents HIF-1α gene transcription, and EF24 reduces HIF-1α post-transcriptionally; though they have similar structures, these two compounds exert their actions through different mechanisms. EF24 can disrupt the microtubule cytoskeleton indirectly and reduce HIF-1α levels dependent on the VHL protein and independent of proteosomal degradation. Moreover, EF24 also shows a slight reduction in HIF-1β protein levels [138]; however, inhibition of the HIF-1β protein occurred at a higher EF24 concentration compared to that dose required for the inhibition of the HIF-1α protein. The transcriptional activation of HIF-associated target genes requires both HIF subunits (-α and -β), so targeting either or both HIF subunits is an effective strategy for HIF inhibitor use either directly or indirectly [139]. These data are in accord with previous study reports showing that curcumin could suppress HIF-1β [140] or HIF-1α [133].

Choi et al evaluated the effects of curcumin administration on HIF-1 expression and activity in cancer cell lines and an animal model of xenograft cancers. Curcumin successfully inactivated HIF-1 activity and its target genes. However, between the two HIF-1 subunits, curcumin could only degrade ARNT in different cell lines without affecting the transcription of HIF-1α. In addition, curcumin induced the proteosomal ARNT degradation through oxidation and ubiquitination pathways. In mice with hepatoma, curcumin attenuated tumor growth and expression of ARNT, erythropoietin and VEGF in the tumor tissues. This critical observation provides the first direct evidence that curcumin has anticancer properties through HIF-1 inhibition via ARNT degradation [140].

This discrepancy between the findings of this latter study [140] with other reports may be due to the differing curcumin preparations. Commercial curcumin often consists of a combination of three distinctive curcuminoids, each of which may have differing effects on HIF-1 levels. Given that HIF-1α has the highest transcriptional activity in the HIF-1 complex, it is a better target compared with ARNT for inhibition of HIF-1 as a therapeutic target. However, many tumor cells have amplified HIF-2α mRNA that is comparable to HIF-1α regarding protein structure and regulation [141,142]. Indeed, HIF-2α can bind to ARNT in order to constitute the HIF-2 transcription complex and contributes to gene regulation in hypoxia. It has been demonstrated that the deletion of HIF1A is unable to prevent vascular tumor progress in VHL-deficient mice due to HIF2A compensation of hypoxic gene expression for the loss of HIF1A activity [143]. The deletion of ARNT prevented tumorigenesis because HIF-1 and HIF-2 act independently through ARNT; therefore, in the context of cancer, focusing on the inhibition of ARNT affects both HIF-1 and HIF-2. Curcumin has been found to suppress of ARNT expression in preclinical studies and therefore may be a promising tumoricidal agent to target HIFs.

Curcumin has been shown to have anti-tumor activity through HIF inactivation in a time-, oxygen-, and concentration-dependent manner. Curcumin treatment enhanced HIF-1α protein amounts in normoxia but conversely led to HIF-1α and HIF-2α degradation in hypoxic conditions. HIF-1βwas decreased at both transcriptional and posttranslational levels in both normoxia and hypoxia post 4 h and 24 h of curcumin incubation in cancer cell lines of liver (Hep3B and HepG2) and breast (MCF-7). Consequently, HIF protein degradation led to a significant reduction in HIF protein function in tumor cells treated under hypoxic conditions [144].

Curcumin also exhibited anti-angiogenic properties by suppressing both basal and hypoxia-induced synthesis of HIF-1α mRNA in corticotroph AtT20 mouse and lactosomatotroph GH3 rat pituitary tumor cells as well as in human pituitary adenoma cell cultures, under hypoxic conditions [145]. Curcumin also inhibited HIF1-α levels in primary cultures of human cancer cells. Therefore, curcumin displayed antiproliferative, pro-apoptotic, and anti-tumor neovascularization actions not only by disruption of HIF-1α protein production and/or stabilization, but also by down-regulation of HIF-1α at the transcriptional level, indicating that curcumin has an inhibitory action on HIF-1α through several mechanisms of action [145].

The thioredoxin (Trx) system, commonly overexpressed in hypoxic tumor cells, also has a positive impact on HIF-1α expression [146]. Trx inhibitors can inhibit activation of HIF-1 and angiogenesis under hypoxic stress. Curcumin can target the Trx system to reduce the intracellular-redox potential, elevate oxidative stress, and finally induces cell death [147]. Curcumin has the potential to be considered as an anticancer drug with its mechanism of action through the Trx system.

Monoamine oxidase A (MAOA), as a mitochondrial enzyme, mediates the development and progression of cancer. MAOA induces EMT and stabilize the HIF-1α, thus increasing the growth, invasion, and propagation of cancer cells [148]. Additionally, the mTOR/HIF-1α axis regulates aerobic glycolysis, which is a metabolic basis for acquired immunity [149]. More recently, Du and Long studied the role of the MAOA/mTOR/HIF-1α pathway in cancer-associated fibroblasts (CAFs)-induced EMT and invasiveness in prostate cancer cells. They also evaluated the protective effect of curcumin on CAF-derived from prostate carcinoma cells. Activated fibroblasts in CAFs or myofibroblasts are the major non-malignant cell type in the cancer stroma and the main indicators of a progressive phenotype for the tumor and its metastasis [150]. CAFs also mediate the EMT process of malignant cells and their progress to stem cells [151]. CAFs may trigger EMT and attack prostate cancer cells via a MAOA/mTOR/HIF-1α pathway in order to increase ROS leading to metastasis and the aggressive behavior of prostate cancer cells. Furthermore, CAFs potentially induce high-expression of CXC chemokine receptor 4 (CXCR4) and the IL-6 receptor. Curcumin prevented CAF-associated aggression and EMT, and

attenuated ROS generation and expression of CXCR4 and IL-6 receptor by ameliorating MAOA/mTOR/HIF-1α signaling in prostate cancer cells. Taken together, these finding suggest that curcumin has the potential to protect against the EMT process in the tumor microenvironment by inhibiting CAF-induced ROS genesis via the MAOA/mTOR/HIF-1α axis [152]. Since, there are multiple cancer-progressive signaling pathways that mediate interactions between various tumoral and non-tumoral cells and CAFs [153], targeting CAFs by curcumin may be a promising therapeutic approach that needs further evaluation.

Curcumin prevents the amplification of VEGF via NFκB regulation. HIF-1α and NFκB regulate the expression of one another, interdependently. The stability of the HIF-1α protein may be disrupted indirectly through p53 levels and increased by curcumin. Tumor suppressor protein p53 prevents hypoxia-stimulated expression of HIF-1α by increasing its proteasomes and ubiquitination [154]. Furthermore, curcumin decreases HIF-1α protein and activity levels, so suppressing VEGF gene expression and hypoxia-induced angiogenesis of cancer cells.

It has been reported that hypoxia-induced HIF-1α in malignant cells leads to chemo and/or radioresistance [144]. In contrast, HIF-1α inhibition reduces human tumor xenograft development, angiogenesis, evasion, and metastasis [155]. Specific HIF-1α knockdown by siRNA alleviated the chemoresistance-related to hypoxia in a human lung cancer cell line [43]. These reports highlight the role of HIF-1α in the resistance to chemotherapy and radiotherapy in human cancers and suggested that targeting HIF-1α might be a promising approach for cancer therapy. Several reports have shown a dose-dependent radiosensitization of different cell lines following curcumin pretreatment before ionizing radiation [156,157]. But in a study performed on hepatoma and breast cancer cell lines, curcumin pretreatment has proapoptotic and antiproliferative effects on clonogenic cell survival, possibly as a result of partial transcription factors degradation. Interestingly, 90% knockdown of HIF-1α protein by siRNA effects radio-sensitivity of these cell lines under hypoxia [144].

Platin-based (DDP) chemotherapy is the basis of treatment of many human tumors and has been show to significantly improve the prognosis of patients. Multidrug resistance (MDR), particularly for DDP regimens, has markedly decreased the efficacy of chemotherapeutic drugs, leading to 5-year survival rate of less than 15% for some patients. This may be contributed to by HIF-1α that was found to be amplified at both the transcriptional and protein levels in the DDP resistant lung cancer A549/DDP cell lines under normoxia. Combination therapy with curcumin and DDP significantly abrogated A549/DDP cells proliferation, disrupted HIF-1α amplification at the protein level, reversed DDP resistance and induced apoptosis through enhancing HIF-1α degradation and activating caspase-3. Down-regulation of HIF-1α–dependent P-glycoprotein via curcumin provides an additional reason to use curcumin as an anti-tumor agent, that may prevent drug resistance and increasing therapeutic potential and therefore efficacy of the current regimens in lung cancer patients [158].

In a recent study, curcumin suppressed the expression of anti-apoptotic protein myeloid cell leukemia-1 (MCL-1), hypoxia-inducible factor 1α (HIF-1α), and vascular endothelial growth factor (VEGF) in primary human hemangioma endothelial cells (HemECs) [159].

12. Conclusion

HIF-target genes are involved in pathogenesis of cancer, fibrosis and vascular disease. Therefore, approaches modifying the hypoxic tumor microenvironment, or targeting the hypoxia-regulated signaling pathways may be effective therapeutic strategies. Anti-tumor drugs that target both HIF-1α and -2α subunits and prevent their dimerization with HIF-1β may have better therapeutic application. Inhibition of HIF-1β/ARNT has received little attention due to its constitutive expression; however, ARNT depletion possibly blocks both HIF-1 and HIF-2. Curcumin has been shown to inhibit ARNT expression and may have a significant activity in preventing the assembly if HIF protein in hypoxia induced cancer and fibrotic conditions.

At present, curcumin is known to be a safe and well tolerated compound showing no toxicity in several clinical trials. Curcumin can inhibit cancer cell growth, development invasion and metastasis under hypoxic and non-hypoxic conditions by targeting HIF-α and/or HIF-β. In this regard, the anti-HIF activity of curcumin in combination with other conventional therapies would have additive and synergistic effects. Although the potency of curcumin is presently under evaluation in multiple clinical trials, its efficacy profile is limited due to its poor absorption and bioavailability, low solubility, and instability as a result of immediate renal excretion and hepatic destruction [160]. Increasing the stability of curcumin derivatives or curcumin-releasing system may overcome this problem and bring this natural compound to the forefront of therapeutic agents for the treatment of human disease in the future [161,162,163].

13. Author contribution

AS devised the study; AB, MM researched the study; sla assisted in reviewing and rewriting the paper. All authors contributed to the manuscript preparation and the final version.

Conflict of interests

Muhammed Majeed is the founder of Sabinsa Corporation and Sami Labs Ltd. Other authors have no direct competing interests to declare.

Funding

No funding was received.

References

[1] H.W. van Laarhoven, J.H. Kaanders, J. Lok, W.J. Peeters, P.F. Rijken, B. Wiering, T.J. Ruers, C.J. Punt, A. Heerschap, A.J. van der Kogel, Hypoxia in relation to vasculature and proliferation in liver metastases in patients with colorectal cancer, Int. J. Radiat. Oncol. Biol. Phys. 64 (2) (2006) 473–482.
[2] W. Jeong, S. Jung, F.W. Bazer, J. Kim, Hypoxia-dependent accumulation of hypoxia-inducible factor-1 alpha induces transient cell cycle arrest in porcine trophectoderm cells, Theriogenology 115 (2018) 9–15.
[3] M. Höckel, P. Vaupel, Biological Consequences of Tumor Hypoxia, Seminars in Oncology, Elsevier, 2001, pp. 36–41.
[4] T. Ozaki, M. Nakamura, T. Ogata, M. Sang, O. Shimozato, The Functional Interplay Between Pro-Oncogenic RUNX2 and Hypoxia-Inducible Factor-1α (HIF-1α) During Hypoxia-Mediated Tumor Progression, Regulation of Signal Transduction in Human Cell Research, Springer, 2018, pp. 85–98.
[5] D. Tarade, M. Ohh, The HIF and other quandaries in VHL disease, Oncogene 37 (2) (2018) 139–147.
[6] E.A. Triantafyllou, E. Georgatsou, I. Mylonis, G. Simos, E. Paraskeva, Expression of AGPAT2, an enzyme involved in the glycerophospholipid/triacylglycerol biosynthesis pathway, is directly regulated by HIF-1 and promotes survival and etoposide resistance of cancer cells under hypoxia, Biochimica Et Biophysica Acta-Mol. Cell Biol. Lipids 1863 (9) (2018) 1142–1152.
[7] V. Wang, D.A. Davis, M. Haque, L.E. Huang, R. Yarchoan, Differential gene up-regulation by hypoxia-inducible factor-1alpha and hypoxia-inducible factor-2alpha in HEK293T cells, Cancer Res. 65 (8) (2005) 3299–3306.
[8] S. Chen, N. Sang, Hypoxia-inducible factor-1: a critical player in the survival strategy of stressed cells, J. Cell. Biochem. 117 (2) (2016) 267–278.
[9] N. Goda, H.E. Ryan, B. Khadivi, W. McNulty, R.C. Rickert, R.S. Johnson, Hypoxia-inducible factor 1α is essential for cell cycle arrest during hypoxia, Mol. Cell. Biol. 23 (1) (2003) 359–369.
[10] J.A. Neubauer, Invited review: physiological and pathophysiological responses to intermittent hypoxia, J. Appl. Physiol. 90 (4) (1985) 1593–1599 (2001).
[11] E. Belaidi, A. Thomas, G. Bourdier, S. Moulin, E. Lemarié, P. Levy, J.-L. Pépin, I. Korichneva, D. Godin-Ribuot, C. Arnaud, Endoplasmic reticulum stress as a novel inducer of hypoxia inducible factor-1 activity: its role in the susceptibility to myocardial ischemia-reperfusion induced by chronic intermittent hypoxia, Int. J. Cardiol. 210 (2016) 45–53.
[12] K.R. Laderoute, J.M. Calaoagan, C. Gustafson-Brown, A.M. Knapp, G.-C. Li, H.L. Mendonca, H.E. Ryan, Z. Wang, R.S. Johnson, The response of c-Jun/AP-1 to chronic hypoxia is hypoxia-inducible factor 1α dependent, Mol. Cell. Biol. 22 (8) (2002) 2515–2523.
[13] C. Werno, J. Zhou, B. Brüne, A23187, ionomycin and thapsigargin upregulate mRNA of HIF-1α via endoplasmic reticulum stress rather than a rise in

intracellular calcium, J. Cell. Physiol. 215 (3) (2008) 708–714.
[14] B. López-Hernández, V. Ceña, I. Posadas, The endoplasmic reticulum stress and the HIF-1 signalling pathways are involved in the neuronal damage caused by chemical hypoxia, Br. J. Pharmacol. 172 (11) (2015) 2838–2851.
[15] H.E. Ryan, J. Lo, R.S. Johnson, HIF-1 alpha is required for solid tumor formation and embryonic vascularization, EMBO J. 17 (11) (1998) 3005–3015.
[16] M. Scortegagna, M.A. Morris, Y. Oktay, M. Bennett, J.A. Garcia, The HIF family member EPAS1/HIF-2alpha is required for normal hematopoiesis in mice, Blood 102 (5) (2003) 1634–1640.
[17] A. Klaus, O. Fathi, T.-W. Tatjana, N. Bruno, K. Oskar, Expression of hypoxia-associated protein HIF-1α in follicular thyroid cancer is associated with distant metastasis, Pathol. Oncol. Res. 24 (2) (2018) 289–296.
[18] S. Rey, L. Schito, B.G. Wouters, S. Eliasof, R.S. Kerbel, Targeting hypoxia-inducible factors for antiangiogenic cancer therapy, Trends Cancer 3 (7) (2017) 529–541.
[19] X. Lu, Y. Kang, Hypoxia and hypoxia-inducible factors: master regulators of metastasis, Clin. Cancer Res. 16 (24) (2010) 5928–5935.
[20] Y. Morine, M. Shimada, T. Utsunomiya, S. Imura, T. Ikemoto, H. Mori, J. Hanaoka, M. Kanamoto, S. Iwahashi, H. Miyake, Hypoxia inducible factor expression in intrahepatic cholangiocarcinoma, Hepatogastroenterology 58 (2011) 110–111 1439-44.
[21] R. Wang, S. Zhou, S. Li, Cancer therapeutic agents targeting hypoxia-inducible factor-1, Curr. Med. Chem. 18 (21) (2011) 3168–3189.
[22] G.L. Semenza, Targeting HIF-1 for cancer therapy, Nat. Rev. Cancer 3 (10) (2003) 721–732.
[23] G.L. Semenza, Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics, Oncogene 29 (5) (2010) 625–634.
[24] G.L. Wang, B.-H. Jiang, E.A. Rue, G.L. Semenza, Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension, Proc. Natl. Acad. Sci. 92 (12) (1995) 5510–5514.
[25] S. Eda, R. Vadde, R. Jinka, Role of Hypoxia-Inducible Factor (HIF) in the Initiation of Cancer and Its Therapeutic Inhibitors, Role of Transcription Factors in Gastrointestinal Malignancies, Springer, 2017, pp. 129–157.
[26] S. Unwith, H. Zhao, L. Hennah, D. Ma, The potential role of HIF on tumour progression and dissemination, Int. J. Cancer 136 (11) (2015) 2491–2503.
[27] B.E. McIntosh, J.B. Hogenesch, C.A. Bradfield, Mammalian per-arnt-sim proteins in environmental adaptation, Annu. Rev. Physiol. 72 (2010) 625–645.
[28] S. Taylor, From Single Cell to Single Molecule: Elucidation of the Intracellular Dynamics of the Hypoxia Inducible Factor (HIF), University of Liverpool, 2015.
[29] C.J. Hu, A. Sataur, L. Wang, H. Chen, M.C. Simon, The N-terminal transactivation domain confers target gene specificity of hypoxia-inducible factors HIF-1alpha and HIF-2alpha, Mol. Biol. Cell 18 (11) (2007) 4528–4542.
[30] M.S. Wiesener, J.S. Jurgensen, C. Rosenberger, C.K. Scholze, J.H. Horstrup, C. Warnecke, S. Mandriota, I. Bechmann, U.A. Frei, C.W. Pugh, P.J. Ratcliffe, S. Bachmann, P.H. Maxwell, K.U. Eckardt, Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs, FASEB J. 17 (2) (2003) 271–273.
[31] K. Hirose, M. Morita, M. Ema, J. Mimura, H. Hamada, H. Fujii, Y. Saijo, O. Gotoh, K. Sogawa, Y. Fujii-Kuriyama, cDNA cloning and tissue-specific expression of a novel basic helix-loop-helix/PAS factor (Arnt2) with close sequence similarity to the aryl hydrocarbon receptor nuclear translocator (Arnt), Mol. Cell. Biol. 16 (4) (1996) 1706–1713.
[32] G. Drutel, M. Kathmann, A. Heron, J.C. Schwartz, J.M. Arrang, Cloning and selective expression in brain and kidney of ARNT2 homologous to the Ah receptor nuclear translocator (ARNT), Biochem. Biophys. Res. Commun. 225 (2) (1996) 333–339.
[33] G.L. Semenza, HIF-1 and mechanisms of hypoxia sensing, Curr. Opin. Cell Biol. 13 (2) (2001) 167–171.
[34] P. Maxwell, K. Salnikow, HIF-1: an oxygen and metal responsive transcription factor, Cancer Biol. Ther. 3 (1) (2004) 29–35.
[35] P. Zhang, Q. Yao, L. Lu, Y. Li, P.J. Chen, C.M. Duan, hypoxia-inducible factor 3 Is an oxygen-dependent transcription activator and regulates a distinct transcriptional response to hypoxia, Cell Rep. 6 (6) (2014) 1110–1121.
[36] S. Hara, J. Hamada, C. Kobayashi, Y. Kondo, N. Imura, Expression and characterization of hypoxia-inducible factor (HIF)-3α in human kidney: suppression of HIF-mediated gene expression by HIF-3α, Biochem. Biophys. Res. Commun. 287 (4) (2001) 808–813.
[37] T. Tanaka, M. Wiesener, W. Bernhardt, K.-U. Eckardt, C. Warnecke, The human HIF (hypoxia-inducible factor)-3α gene is a HIF-1 target gene and may modulate hypoxic gene induction, Biochem. J. 424 (1) (2009) 143–151.
[38] M. Ivan, K. Kondo, H. Yang, W. Kim, J. Valiando, M. Ohh, A. Salic, J.M. Asara, W.S. Lane, W.G. Kaelin Jr, HIFα targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing, Science 292 (5516) (2001) 464–468.
[39] C.M. Robinson, M. Ohh, The multifaceted von Hippel–Lindau tumour suppressor protein, FEBS Lett. 588 (16) (2014) 2704–2711.
[40] G.N. Masoud, W. Li, HIF-1α pathway: role, regulation and intervention for cancer therapy, Acta Pharm. Sin. B 5 (5) (2015) 378–389.
[41] D.M. Katschinski, L. Le, D. Heinrich, K.F. Wagner, T. Hofer, S.G. Schindler, R.H. Wenger, Heat induction of the unphosphorylated form of hypoxia-inducible factor-1α is dependent on heat shock protein-90 activity, J. Biol. Chem. 277 (11) (2002) 9262–9267.
[42] J.S. Isaacs, Y.-J. Jung, E.G. Mimnaugh, A. Martinez, F. Cuttitta, L.M. Neckers, Hsp90 regulates a von Hippel Lindau-independent hypoxia-inducible factor-1α-degradative pathway, J. Biol. Chem. 277 (33) (2002) 29936–29944.
[43] S. Schnitzer, T. Schmid, J. Zhou, B. Brüne, Hypoxia and HIF-1α protect A549 cells from drug-induced apoptosis, Cell Death Differ. 13 (9) (2006) 1611.
[44] F. Agani, B.H. Jiang, Oxygen-independent regulation of HIF-1: novel involvement of PI3K/AKT/mTOR pathway in cancer, Curr. Cancer Drug Targets 13 (3) (2013) 245–251.
[45] A. Bahrami, M. Khazaei, S. Shahidsales, S.M. Hassanian, M. Hasanzadeh, M. Maftouh, G.A. Ferns, A. Avan, The therapeutic potential of PI3K/akt/mTOR inhibitors in breast cancer: rational and progress, J. Cell. Biochem. 119 (1) (2018) 213–222.
[46] A. Bahrami, M. Hasanzadeh, S.M. Hassanian, S. ShahidSales, M. Ghayour-Mobarhan, G.A. Ferns, A. Avan, The potential value of the PI3K/akt/mTOR signaling pathway for assessing prognosis in cervical cancer and as a target for therapy, J. Cell. Biochem. 118 (12) (2017) 4163–4169.
[47] M. Alvarez-Tejado, S. Naranjo-Suarez, C. Jimenez, A.C. Carrera, M.O. Landazuri, L. del Peso, Hypoxia induces the activation of the phosphatidylinositol 3-kinase/akt cell survival pathway in PC12 cells: protective role in apoptosis, J. Biol. Chem. 276 (25) (2001) 22368–22374.
[48] N. Sang, D.P. Stiehl, J. Bohensky, I. Leshchinsky, V. Srinivas, J. Caro, MAPK signaling up-regulates the activity of hypoxia-inducible factors by its effects on p300, J. Biol. Chem. 278 (16) (2003) 14013–14019.
[49] D.E. Richard, E. Berra, E. Gothie, D. Roux, J. Pouyssegur, p42/p44 mitogen-activated protein kinases phosphorylate hypoxia-inducible factor 1alpha (HIF-1alpha) and enhance the transcriptional activity of HIF-1, J. Biol. Chem. 274 (46) (1999) 32631–32637.
[50] R. Fukuda, K. Hirota, F. Fan, Y. Do Jung, L.M. Ellis, G.L. Semenza, Insulin-like growth factor 1 induces hypoxia-inducible factor 1-mediated vascular endothelial growth factor expression, which is dependent on MAP kinase and phosphatidylinositol 3-kinase signaling in colon cancer cells, J. Biol. Chem. 277 (41) (2002) 38205–38211.
[51] P.W. Conrad, T.L. Freeman, D. Beitner-Johnson, D.E. Millhorn, EPAS1 trans-activation during hypoxia requires p42/p44 MAPK, J. Biol. Chem. 274 (47) (1999) 33709–33713.
[52] N. Burrows, M. Babur, J. Resch, S. Ridsdale, M. Mejin, E.J. Rowling, G. Brabant, K.J. Williams, GDC-0941 inhibits metastatic characteristics of thyroid carcinomas by targeting both the phosphoinositide-3 kinase (PI3K) and hypoxia-inducible factor-1α (HIF-1α) pathways, J. Clin. Endocrinol. Metab. 96 (12) (2011) E1934–E1943.
[53] G.L. Semenza, HIF-1 and human disease: one highly involved factor, Genes Dev. 14 (16) (2000) 1983–1991.
[54] S.H. Liao, X.Y. Zhao, Y.H. Han, J. Zhang, L.S. Wang, L. Xia, K.W. Zhao, Y. Zheng, M. Guo, G.Q. Chen, Proteomics-based identification of two novel direct targets of hypoxia-inducible factor-1 and their potential roles in migration/invasion of cancer cells, Proteomics 9 (15) (2009) 3901–3912.
[55] Z.B. Han, H. Ren, H. Zhao, Y. Chi, K. Chen, B. Zhou, Y.J. Liu, L. Zhang, B. Xu, B. Liu, R. Yang, Z.C. Han, Hypoxia-inducible factor (HIF)-1 alpha directly enhances the transcriptional activity of stem cell factor (SCF) in response to hypoxia and epidermal growth factor (EGF), Carcinogenesis 29 (10) (2008) 1853–1861.
[56] B.D. Kelly, S.F. Hackett, K. Hirota, Y. Oshima, Z. Cai, S. Berg-Dixon, A. Rowan, Z. Yan, P.A. Campochiaro, G.L. Semenza, Cell type-specific regulation of angiogenic growth factor gene expression and induction of angiogenesis in nonischemic tissue by a constitutively active form of hypoxia-inducible factor 1, Circ. Res. 93 (11) (2003) 1074–1081.
[57] L.L. Nikitenko, D.M. Smith, R. Bicknell, M.C. Rees, Transcriptional regulation of the CRLR gene in human microvascular endothelial cells by hypoxia, FASEB J. 17 (11) (2003) 1499–1501.
[58] Q. Sun, H. Zhou, N.O. Binmadi, J.R. Basile, Hypoxia-inducible factor-1-mediated regulation of semaphorin 4D affects tumor growth and vascularity, J. Biol. Chem. 284 (46) (2009) 32066–32074.
[59] M.H. Yang, M.Z. Wu, S.H. Chiou, P.M. Chen, S.Y. Chang, C.J. Liu, S.C. Teng, K.J. Wu, Direct regulation of TWIST by HIF-1alpha promotes metastasis, Nat. Cell Biol. 10 (3) (2008) 295–305.
[60] B. Krishnamachary, D. Zagzag, H. Nagasawa, K. Rainey, H. Okuyama, J.H. Baek, G.L. Semenza, Hypoxia-inducible factor-1-dependent repression of E-cadherin in von Hippel-Lindau tumor suppressor-null renal cell carcinoma mediated by TCF3, ZFHX1A, and ZFHX1B, Cancer Res. 66 (5) (2006) 2725–2731.
[61] E.A. O'Toole, R. van Koningsveld, M. Chen, D.T. Woodley, Hypoxia induces epidermal keratinocyte matrix metalloproteinase-9 secretion via the protein kinase C pathway, J. Cell. Physiol. 214 (1) (2008) 47–55.
[62] M. Obach, A. Navarro-Sabate, J. Caro, X. Kong, J. Duran, M. Gomez, J.C. Perales, F. Ventura, J.L. Rosa, R. Bartrons, 6-Phosphofructo-2-kinase (pfkfb3) gene promoter contains hypoxia-inducible factor-1 binding sites necessary for transactivation in response to hypoxia, J. Biol. Chem. 279 (51) (2004) 53562–53570.
[63] J.W. Kim, I. Tchernyshyov, G.L. Semenza, C.V. Dang, HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia, Cell Metab. 3 (3) (2006) 177–185.
[64] M.S. Ullah, A.J. Davies, A.P. Halestrap, The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism, J. Biol. Chem. 281 (14) (2006) 9030–9037.
[65] A. Gabrielli, E.V. Avvedimento, T. Krieg, N. Scleroderma, Engl. J. Med. 360 (19) (2009) 1989–2003.
[66] D.M. Gilkes, S. Bajpai, P. Chaturvedi, D. Wirtz, G.L. Semenza, Hypoxia-inducible factor 1 (HIF-1) promotes extracellular matrix remodeling under hypoxic conditions by inducing P4HA1, P4HA2, and PLOD2 expression in fibroblasts, J. Biol. Chem. 288 (15) (2013) 10819–10829.
[67] B.K. Nayak, K. Shanmugasundaram, W.E. Friedrichs, R.C. Cavaglierii, M. Patel, J. Barnes, K. Block, HIF-1 mediates renal fibrosis in OVE26 type 1 diabetic mice, Diabetes 65 (5) (2016) 1387–1397.
[68] S. Bonnet, E.D. Michelakis, C.J. Porter, M.A. Andrade-Navarro, B. Thebaud, S. Bonnet, A. Haromy, G. Harry, R. Moudgil, M.S. McMurtry, E.K. Weir,

S.L. Archer, An abnormal mitochondrial-hypoxia inducible factor-1alpha-Kv channel pathway disrupts oxygen sensing and triggers pulmonary arterial hypertension in fawn hooded rats: similarities to human pulmonary arterial hypertension, Circulation 113 (22) (2006) 2630–2641.
[69] R.M. Tuder, M. Chacon, L. Alger, J. Wang, L. Taraseviciene-Stewart, Y. Kasahara, C.D. Cool, A.E. Bishop, M. Geraci, G.L. Semenza, M. Yacoub, J.M. Polak, N.F. Voelkel, Expression of angiogenesis-related molecules in plexiform lesions in severe pulmonary hypertension: evidence for a process of disordered angiogenesis, J. Pathol. 195 (3) (2001) 367–374.
[70] J. Wang, X. Fu, K. Yang, Q. Jiang, Y. Chen, J. Jia, X. Duan, E.W. Wang, J. He, P. Ran, N. Zhong, G.L. Semenza, W. Lu, Hypoxia inducible factor-1-dependent up-regulation of BMP4 mediates hypoxia-induced increase of TRPC expression in PASMCs, Cardiovasc. Res. 107 (1) (2015) 108–118.
[71] C. Veith, D. Zakrzewicz, B.K. Dahal, Z. Balint, K. Murmann, M. Wygrecka, W. Seeger, R.T. Schermuly, N. Weissmann, G. Kwapiszewska, Hypoxia- or PDGF-BB-dependent paxillin tyrosine phosphorylation in pulmonary hypertension is reversed by HIF-1alpha depletion or imatinib treatment, Thromb. Haemost. 112 (6) (2014) 1288–1303.
[72] Y. Kitajima, T. Ide, T. Ohtsuka, K. Miyazaki, Induction of hepatocyte growth factor activator gene expression under hypoxia activates the hepatocyte growth factor/c-met system via hypoxia inducible factor-1 in pancreatic cancer, Cancer Sci. 99 (7) (2008) 1341–1347.
[73] D.J. Ceradini, A.R. Kulkarni, M.J. Callaghan, O.M. Tepper, N. Bastidas, M.E. Kleinman, J.M. Capla, R.D. Galiano, J.P. Levine, G.C. Gurtner, Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1, Nat. Med. 10 (8) (2004) 858–864.
[74] A. Sahebkar, Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? Biofactors 39 (2) (2013) 197–208.
[75] S. Prasad, S.C. Gupta, A.K. Tyagi, B.B. Aggarwal, Curcumin, a component of golden spice: from bedside to bench and back, Biotechnol. Adv. 32 (6) (2014) 1053–1064.
[76] A. Siviero, E. Gallo, V. Maggini, L. Gori, A. Mugelli, F. Firenzuoli, A. Vannacci, Curcumin, a golden spice with a low bioavailability, J. Herbal Med. 5 (2) (2015) 57–70.
[77] Y. Panahi, M.S. Hosseini, N. Khalili, E. Naimi, M. Majeed, A. Sahebkar, Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis, Clin. Nutr. 34 (6) (2015) 1101–1108.
[78] Y. Panahi, G.H. Alishiri, S. Parvin, A. Sahebkar, Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: results of a randomized controlled trial, J. Diet Suppl. 13 (2) (2016) 209–220.
[79] Y. Panahi, M. Ghanei, A. Hajhashemi, A. Sahebkar, Effects of curcuminoids-piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: a randomized controlled trial, J. Diet Suppl. 13 (1) (2016) 93–105.
[80] A. Sahebkar, M.C. Serban, S. Ursoniu, M. Banach, Effect of curcuminoids on oxidative stress: a systematic review and meta-analysis of randomized controlled trials, J. Funct. Foods 18 (2015) 898–909.
[81] H. Mirzaei, G. Naseri, R. Rezaee, M. Mohammadi, Z. Banikazemi, H.R. Mirzaei, H. Salehi, M. Peyvandi, J.M. Pawelek, A. Sahebkar, Curcumin: a new candidate for melanoma therapy? Int. J. Cancer 139 (8) (2016) 1683–1695.
[82] R.M. Marjaneh, F. Rahmani, S.M. Hassanian, N. Rezaei, M. Hashemzehi, A. Bahrami, F. Ariakia, H. Fiuji, A. Sahebkar, A. Avan, M. Khazaei, Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer, J. Cell. Physiol. 233 (10) (2018) 6785–6798.
[83] B. Cheppudira, M. Fowler, L. McGhee, A. Greer, A. Mares, L. Petz, D. Devore, D.R. Loyd, J.L. Clifford, Curcumin: a novel therapeutic for burn pain and wound healing, Expert Opin. Investig. Drugs 22 (10) (2013) 1295–1303.
[84] A. Sahebkar, Y. Henrotin, Analgesic efficacy and safety of curcuminoids in clinical practice: a systematic review and meta-analysis of randomized controlled trials, Pain Med. 17 (6) (2016) 1192–1202.
[85] F. Keihanian, A. Saeidinia, R.K. Bagheri, T.P. Johnston, A. Sahebkar, Curcumin, hemostasis, thrombosis, and coagulation, J. Cell. Physiol. 233 (6) (2018) 4497–4511.
[86] E. Abdollahi, A.A. Momtazi, T.P. Johnston, A. Sahebkar, Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: a nature-made jack-of-all-trades? J. Cell. Physiol. 233 (2) (2018) 830–848.
[87] Y. Panahi, N. Khalili, E. Sahebi, S. Namazi, L.E. Simental-Mendia, M. Majeed, A. Sahebkar, Effects of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in patients with type 2 diabetes mellitus: a randomized double-blind placebo-controlled trial, Drug Res. (Stuttg.) 68 (7) (2018) 403–409.
[88] N.A. Zabihi, M. Pirro, T.P. Johnston, A. Sahebkar, Is there a role for curcumin supplementation in the treatment of Non-alcoholic fatty liver disease? The data suggest yes, Curr. Pharm. Des. 23 (7) (2017) 969–982.
[89] S. Rahmani, S. Asgary, G. Askari, M. Keshvari, M. Hatamipour, A. Feizi, A. Sahebkar, Treatment of Non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial, Phytother. Res. 30 (9) (2016) 1540–1548.
[90] M. Xie, D. Fan, Z. Zhao, Z. Li, G. Li, Y. Chen, X. He, A. Chen, J. Li, X. Lin, M. Zhi, Y. Li, P. Lan, Nano-curcumin prepared via supercritical: improved anti-bacterial, anti-oxidant and anti-cancer efficacy, Int. J. Pharm. 496 (2) (2015) 732–740.
[91] A.F.G. Cicero, A. Colletti, G. Bajraktari, O. Descamps, D.M. Djuric, M. Ezhov, Z. Fras, N. Katsiki, M. Langlois, G. Latkovskis, D.B. Panagiotakos, G. Paragh, D.P. Mikhailidis, O. Mitchenko, B. Paulweber, D. Pella, C. Pitsavos, Z. Reiner, K.K. Ray, M. Rizzo, A. Sahebkar, M.C. Serban, L.S. Sperling, P.P. Toth, D. Vinereanu, M. Vrablik, N.D. Wong, M. Banach, lipid lowering nutraceuticals in clinical practice: position paper from an international lipid expert panel, Arch. Med. Sci. 13 (5) (2017) 965–1005.
[92] Y. Panahi, N. Khalili, M.S. Hosseini, M. Abbasinazari, A. Sahebkar, Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial, Complement. Ther. Med. 22 (5) (2014) 851–857.
[93] S. Ganjali, C.N. Blesso, M. Banach, M. Pirro, M. Majeed, A. Sahebkar, Effects of curcumin on HDL functionality, Pharmacol. Res. 119 (2017) 208–218.
[94] Y. Panahi, P. Kianpour, R. Mohtashami, R. Jafari, L.E. Simental-Mendia, A. Sahebkar, Curcumin lowers serum lipids and uric acid in subjects with non-alcoholic fatty liver disease: a randomized controlled trial, J. Cardiovasc. Pharmacol. 68 (3) (2016) 223–229.
[95] Y. Panahi, A. Sahebkar, S. Parvin, A. Saadat, A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications, Ann. Clin. Biochem. 49 (Pt 6) (2012) 580–588.
[96] M.S. Karimian, M. Pirro, M. Majeed, A. Sahebkar, Curcumin as a natural regulator of monocyte chemoattractant protein-1, Cytokine Growth Factor Rev. 33 (2017) 55–63.
[97] A. Sahebkar, A.F.G. Cicero, L.E. Simental-Mendia, B.B. Aggarwal, S.C. Gupta, Curcumin downregulates human tumor necrosis factor-alpha levels: a systematic review and meta-analysis ofrandomized controlled trials, Pharmacol. Res. 107 (2016) 234–242.
[98] A.A. Momtazi, A. Sahebkar, Difluorinated curcumin: a promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile, Curr. Pharm. Des. 22 (28) (2016) 4386–4397.
[99] A.A. Momtazi, F. Shahabipour, S. Khatibi, T.P. Johnston, M. Pirro, A. Sahebkar, Curcumin as a MicroRNA regulator in cancer: a review, Rev. Physiol. Biochem. Pharmacol. 171 (2016) 1–38.
[100] D. Perrone, F. Ardito, G. Giannatempo, M. Dioguardi, G. Troiano, L. Lo Russo, DE Lillo A, L. Laino, L. Lo Muzio, Biological and therapeutic activities, and anticancer properties of curcumin, Exp. Ther. Med. 10 (5) (2015) 1615–1623.
[101] V.P. Menon, A.R. Sudheer, Antioxidant and anti-inflammatory properties of curcumin, Adv. Exp. Med. Biol. 595 (2007) 105–125.
[102] X. Xu, Y. Cai, Y. Yu, Effects of a novel curcumin derivative on the functions of kidney in streptozotocin-induced type 2 diabetic rats, Inflammopharmacology 26 (5) (2018) 1257–1264.
[103] H. Chen, X. Yang, K. Lu, C. Lu, Y. Zhao, S. Zheng, J. Li, Z. Huang, Y. Huang, Y. Zhang, G. Liang, Inhibition of high glucose-induced inflammation and fibrosis by a novel curcumin derivative prevents renal and heart injury in diabetic mice, Toxicol. Lett. 278 (2017) 48–58.
[104] B.H. Kim, E.S. Lee, R. Choi, J. Nawaboot, M.Y. Lee, E.Y. Lee, H.S. Kim, C.H. Chung, Protective effects of curcumin on renal oxidative stress and lipid metabolism in a rat model of type 2 diabetic nephropathy, Yonsei Med J 57 (3) (2016) 664–673.
[105] C.S. Beevers, S. Huang, Pharmacological and clinical properties of curcumin, Bot.: Targets Ther. 1 (5) (2011).
[106] B.B. Aggarwal, A. Kumar, M.S. Aggarwal, S. Shishodia, Curcumin derived from turmeric (curcuma longa): a spice for all seasons, Phytopharm. Cancer Chemoprev. 23 (2005) 351–387.
[107] A. Soltani, A. Salmaninejad, M. Jalili-Nik, A. Soleimani, H. Javid, S.I. Hashemy, A. Sahebkar, 5'-adenosine monophosphate-activated protein kinase: a potential target for disease prevention by curcumin, J. Cell. Physiol. (2018), https://doi.org/10.1002/jcp.27192 Epub ahead of print.
[108] C.T. Tu, Q.Y. Yao, B.L. Xu, J.Y. Wang, C.H. Zhou, S.C. Zhang, Protective effects of curcumin against hepatic fibrosis induced by carbon tetrachloride: modulation of high-mobility group box 1, Toll-like receptor 4 and 2 expression, Food Chem. Toxicol. 50 (9) (2012) 3343–3351.
[109] W.M. Weber, L.A. Hunsaker, C.N. Roybal, E.V. Bobrovnikova-Marjon, S.F. Abcouwer, R.E. Royer, L.M. Deck, D.L. Vander, Jagt, activation of NFκB is inhibited by curcumin and related enones, Bioorg. Med. Chem. 14 (7) (2006) 2450–2461.
[110] Y.S. Lee, J.W. Kim, O. Osborne, D.Y. Oh, R. Sasik, S. Schenk, A. Chen, H. Chung, A. Murphy, S.M. Watkins, O. Quehenberger, R.S. Johnson, J.M. Olefsky, Increased adipocyte O2 consumption triggers HIF-1alpha, causing inflammation and insulin resistance in obesity, Cell 157 (6) (2014) 1339–1352.
[111] K. Sun, J. Tordjman, K. Clement, P.E. Scherer, Fibrosis and adipose tissue dysfunction, Cell Metab. 18 (4) (2013) 470–477.
[112] I.J. Neeland, A.T. Turer, C.R. Ayers, T.M. Powell-Wiley, G.L. Vega, R. Farzaneh-Far, S.M. Grundy, A. Khera, D.K. McGuire, J.A. de Lemos, Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults, Jama 308 (11) (2012) 1150–1159.
[113] P. Trayhurn, Hypoxia and adipocyte physiology: implications for adipose tissue dysfunction in obesity, Annu. Rev. Nutr. 34 (2014) 207–236.
[114] Z. Qiu, S. Zhang, A. Li, J. Yu, N. Li, F. Huang, B. Liu, The role of curcumin in disruption of HIF-1α accumulation to alleviate adipose fibrosis via AMPK-mediated mTOR pathway in high-fat diet fed mice, J. Funct. Foods 33 (2017) 155–165.
[115] A. Pellicoro, P. Ramachandran, J.P. Iredale, J.A. Fallowfield, Liver fibrosis and repair: immune regulation of wound healing in a solid organ, nature reviews, Immunology 14 (3) (2014) 181–194.
[116] Y. Zhao, X. Ma, J. Wang, X. He, Y. Hu, P. Zhang, R. Wang, R. Li, M. Gong, S. Luo, X. Xiao, Curcumin protects against CCl4-induced liver fibrosis in rats by inhibiting HIF-1alpha through an ERK-dependent pathway, Molecules 19 (11) (2014) 18767–18780 (Basel, Switzerland).
[117] L. She, D. Xu, Z. Wang, Y. Zhang, Q. Wei, J. Aa, G. Wang, B. Liu, Y. Xie, Curcumin inhibits hepatic stellate cell activation via suppression of succinate-associated HIF-1alpha induction, Mol. Cell. Endocrinol. 476 (2018) 129–138.
[118] F. Zhang, Z. Zhang, L. Chen, D. Kong, X. Zhang, C. Lu, Y. Lu, S. Zheng, Curcumin

attenuates angiogenesis in liver fibrosis and inhibits angiogenic properties of hepatic stellate cells, J. Cell. Mol. Med. 18 (7) (2014) 1392–1406.
[119] S.-B. Catrina, K. Okamoto, T. Pereira, K. Brismar, L. Poellinger, Hyperglycemia regulates hypoxia-inducible factor-1α protein stability and function, Diabetes 53 (12) (2004) 3226–3232.
[120] K. Malmberg, A. Norhammar, H. Wedel, L. Ryden, Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction - long-term results from the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study, Circulation 99 (20) (1999) 2626–2632.
[121] T.N. Milovanova, V.M. Bhopale, E.M. Sorokina, J.S. Moore, T.K. Hunt, M. Hauer-Jensen, O.C. Velazquez, S.R. Thom, Lactate stimulates vasculogenic stem cells via the thioredoxin system and engages an autocrine activation loop involving hypoxia-inducible factor 1, Mol. Cell. Biol. 28 (20) (2008) 6248–6261.
[122] T.N. Milovanova, V.M. Bhopale, E.M. Sorokina, J.S. Moore, T.K. Hunt, M. Hauer-Jensen, O.C. Velazquez, S.R. Thom, Hyperbaric oxygen stimulates vasculogenic stem cell growth and differentiation in vivo, J. Appl. Physiol. 106 (2) (1985) 711–728 (2009).
[123] K.A. Gallagher, Z.J. Liu, M. Xiao, H. Chen, L.J. Goldstein, D.G. Buerk, A. Nedeau, S.R. Thom, O.C. Velazquez, Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha, J. Clin. Invest. 117 (5) (2007) 1249–1259.
[124] N. Parsamanesh, M. Moossavi, A. Bahrami, A.E. Butler, A. Sahebkar, Therapeutic potential of curcumin in diabetic complications, Pharmacol. Res. 136 (2018) 181–193.
[125] V. Kant, D. Kumar, R. Prasad, A. Gopal, N.N. Pathak, P. Kumar, S.K. Tandan, Combined effect of substance P and curcumin on cutaneous wound healing in diabetic rats, J. Surg. Res. 212 (2017) 130–145.
[126] V. Kant, A. Gopal, D. Kumar, N.N. Pathak, M. Ram, B.L. Jangir, S.K. Tandan, D. Kumar, Curcumin-induced angiogenesis hastens wound healing in diabetic rats, J. Surg. Res. 193 (2) (2015) 978–988.
[127] S. Kizaka-Kondoh, M. Inoue, H. Harada, M. Hiraoka, Tumor hypoxia: a target for selective cancer therapy, Cancer Sci 94 (12) (2003) 1021–1028.
[128] H. Yasuda, Solid tumor physiology and hypoxia-induced chemo/radio-resistance: novel strategy for cancer therapy: nitric oxide donor as a therapeutic enhancer, Nitric Oxide-Biol. Chem. 19 (2) (2008) 205–216.
[129] P. Vaupel, A. Mayer, Hypoxia in cancer: significance and impact on clinical outcome, Cancer Metastasis Rev. 26 (2) (2007) 225–239.
[130] D.E. Swinson, J.L. Jones, D. Richardson, C. Wykoff, H. Turley, J. Pastorek, N. Taub, A.L. Harris, K.J. O'byrne, Carbonic anhydrase IX expression, a novel surrogate marker of tumor hypoxia, is associated with a poor prognosis in non–-small-cell lung cancer, J. Clin. Oncol. 21 (3) (2003) 473–482.
[131] S.-S. Zheng, X.-H. Chen, X. Yin, B.-H. Zhang, Prognostic significance of HIF-1α expression in hepatocellular carcinoma: a meta-analysis, PloS One 8 (6) (2013) e65753.
[132] Q. Zhang, X. Bai, W. Chen, T. Ma, Q. Hu, C. Liang, S. Xie, C. Chen, L. Hu, S. Xu, T. Liang, Wnt/beta-catenin signaling enhances hypoxia-induced epithelial-mesenchymal transition in hepatocellular carcinoma via crosstalk with hif-1alpha signaling, Carcinogenesis 34 (5) (2013) 962–973.
[133] M.K. Bae, S.H. Kim, J.W. Jeong, Y.M. Lee, H.S. Kim, S.R. Kim, I. Yun, S.K. Bae, K.W. Kim, Curcumin inhibits hypoxia-induced angiogenesis via down-regulation of HIF-1, Oncol. Rep. 15 (6) (2006) 1557–1562.
[134] W. Duan, Y. Chang, R. Li, Q. Xu, J. Lei, C. Yin, T. Li, Y. Wu, Q. Ma, X. Li, Curcumin inhibits hypoxia inducible factor1alphainduced epithelialmesenchymal transition in HepG2 hepatocellular carcinoma cells, Mol. Med. Rep. 10 (5) (2014) 2505–2510.
[135] B. Yoysungnoen, P. Bhattarakosol, S. Patumraj, C. Changtam, Effects of tetrahydrocurcumin on hypoxia-inducible factor-1alpha and vascular endothelial growth factor expression in cervical cancer cell-induced angiogenesis in nude mice, Biomed. Res. Int. 2015 (2015) 391748.
[136] C. Guo, L. Wang, B. Jiang, D. Shi, Bromophenol curcumin analog BCA-5 exerts an antiangiogenic effect through the HIF-1α/VEGF/Akt signaling pathway in human umbilical vein endothelial cells, Anticancer Drugs (2018), https://doi.org/10.1097/CAD.0000000000000671 Epub ahead of print.
[137] V. Russo, A. Rago, B. Pannone, F. Di Meo, A.A. Papa, M.C. Mayer, A. Spasiano, M.G. Russo, P. Golino, R. Calabro, G. Nigro, Early electrocardiographic evaluation of atrial fibrillation risk in beta-thalassemia major patients, Int. J. Hematol. 93 (4) (2011) 446–451.
[138] S.L. Thomas, D. Zhong, W. Zhou, S. Malik, D. Liotta, J.P. Snyder, E. Hamel, P. Giannakakou, EF24, a novel curcumin analog, disrupts the microtubule cytoskeleton and inhibits HIF-1, Cell Cycle 7 (15) (2008) 2409–2417 (Georgetown, Tex.).
[139] G.L. Semenza, Evaluation of HIF-1 inhibitors as anticancer agents, Drug Discov. Today 12 (2007) 19–20 853-9.
[140] H. Choi, Y.S. Chun, S.W. Kim, M.S. Kim, J.W. Park, Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: a mechanism of tumor growth inhibition, Mol. Pharmacol. 70 (5) (2006) 1664–1671.
[141] J. Peng, L. Zhang, L. Drysdale, G.H. Fong, The transcription factor EPAS-1/hypoxia-inducible factor 2alpha plays an important role in vascular remodeling, PNAS 97 (15) (2000) 8386–8391.
[142] M.S. Wiesener, H. Turley, W.E. Allen, C. Willam, K.U. Eckardt, K.L. Talks, S.M. Wood, K.C. Gatter, A.L. Harris, C.W. Pugh, P.J. Ratcliffe, P.H. Maxwell, Induction of endothelial PAS domain protein-1 by hypoxia: characterization and comparison with hypoxia-inducible factor-1alpha, Blood 92 (7) (1998) 2260–2268.
[143] E.B. Rankin, J. Rha, T.L. Unger, C.H. Wu, H.P. Shutt, R.S. Johnson, M.C. Simon, B. Keith, V.H. Haase, Hypoxia-inducible factor-2 regulates vascular tumorigenesis in mice, Oncogene 27 (40) (2008) 5354–5358.
[144] M. Strofer, W. Jelkmann, R. Depping, 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] 187 (7) (2011) 393–400.
[145] B. Shan, C. Schaaf, A. Schmidt, K. Lucia, M. Buchfelder, M. Losa, D. Kuhlen, J. Kreutzer, M.J. Perone, E. Arzt, G.K. Stalla, U. Renner, Curcumin suppresses HIF1A synthesis and VEGFA release in pituitary adenomas, J. Endocrinol. 214 (3) (2012) 389–398.
[146] F. Dal Piaz, A. Braca, M.A. Belisario, N. De Tommasi, Thioredoxin system modulation by plant and fungal secondary metabolites, Curr. Med. Chem. 17 (5) (2010) 479–494.
[147] W. Cai, B. Zhang, D. Duan, J. Wu, J. Fang, Curcumin targeting the thioredoxin system elevates oxidative stress in HeLa cells, Toxicol. Appl. Pharmacol. 262 (3) (2012) 341–348.
[148] J.B. Wu, C. Shao, X. Li, Q. Li, P. Hu, C. Shi, Y. Li, Y.T. Chen, F. Yin, C.P. Liao, B.L. Stiles, H.E. Zhau, J.C. Shih, L.W. Chung, Monoamine oxidase a mediates prostate tumorigenesis and cancer metastasis, J. Clin. Invest. 124 (7) (2014) 2891–2908.
[149] S.C. Cheng, J. Quintin, R.A. Cramer, K.M. Shepardson, S. Saeed, V. Kumar, E.J. Giamarellos-Bourboulis, J.H. Martens, N.A. Rao, A. Aghajanirefah, G.R. Manjeri, Y. Li, D.C. Ifrim, R.J. Arts, B.M. van der Veer, P.M. Deen, C. Logie, L.A. O'Neill, P. Willems, F.L. van de Veerdonk, J.W. van der Meer, A. Ng, L.A. Joosten, C. Wijmenga, H.G. Stunnenberg, R.J. Xavier, M.G. Netea, mTOR- and HIF-1alpha-mediated aerobic glycolysis as metabolic basis for trained immunity, Science 345 (6204) (2014) 1250684.
[150] A. Bahrami, M. Khazaei, S.M. Hassanian, S. ShahidSales, M. Joudi-Mashhad, M. Maftouh, M.H. Jazayeri, M.R. Parizade, G.A. Ferns, A. Avan, Targeting the tumor microenvironment as a potential therapeutic approach in colorectal cancer: rational and progress, J. Cell. Physiol. 233 (4) (2018) 2928–2936.
[151] A. Bahrami, M. Khazaei, F. Bagherieh, M. Ghayour-Mobarhan, M. Maftouh, S.M. Hassanian, A. Avan, Targeting stroma in pancreatic cancer: promises and failures of targeted therapies, J. Cell. Physiol. 232 (11) (2017) 2931–2937.
[152] Y. Du, Q. Long, L. Zhang, Y. Shi, X. Liu, X. Li, B. Guan, Y. Tian, X. Wang, L. Li, D. He, Curcumin inhibits cancer-associated fibroblast-driven prostate cancer invasion through MAOA/mTOR/HIF-1alpha signaling, Int. J. Oncol. 47 (6) (2015) 2064–2072.
[153] A. Bahrami, S.M. Hassanian, M. Khazaei, M. Hasanzadeh, S. Shahidsales, M. Maftouh, G.A. Ferns, A. Avan, The therapeutic potential of targeting tumor microenvironment in breast cancer: rational strategies and recent progress, J. Cell. Biochem. 119 (1) (2018) 111–122.
[154] R. Ravi, B. Mookerjee, Z.M. Bhujwalla, C.H. Sutter, D. Artemov, Q. Zeng, L.E. Dillehay, A. Madan, G.L. Semenza, A. Bedi, Regulation of tumor angiogenesis by p53-induced degradation of hypoxia-inducible factor 1alpha, Genes Dev. 14 (1) (2000) 34–44.
[155] D. Liao, R.S. Johnson, Hypoxia: a key regulator of angiogenesis in cancer, Cancer Metastasis Rev. 26 (2) (2007) 281–290.
[156] P. Javvadi, A.T. Segan, S.W. Tuttle, C. Koumenis, The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway, Mol. Pharmacol. 73 (5) (2008) 1491–1501.
[157] S.K. Sandur, A. Deorukhkar, M.K. Pandey, A.M. Pabon, S. Shentu, S. Guha, B.B. Aggarwal, S. Krishnan, Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NF-kappaB activity, Int. J. Radiat. Oncol. Biol. Phys. 75 (2) (2009) 534–542.
[158] M.X. Ye, Y.L. Zhao, Y. Li, Q. Miao, Z.K. Li, X.L. Ren, L.Q. Song, H. Yin, J. Zhang, Curcumin reverses cis-platin resistance and promotes human lung adenocarcinoma A549/DDP cell apoptosis through HIF-1alpha and caspase-3 mechanisms, Phytomedicine 19 (8-9) (2012) 779–787.
[159] S. Lou, Y. Wang, Z. Yu, K. Guan, Q. Kan, Curcumin induces apoptosis and inhibits proliferation in infantile hemangioma endothelial cells via downregulation of MCL-1 and HIF-1alpha, Medicine (Baltimore) 97 (7) (2018) e9562.
[160] Y. Panahi, A. Saadat, F. Beiraghdar, A. Sahebkar, 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, Phytother. Res. 28 (10) (2014) 1461–1467.
[161] M. Mehanny, R.M. Hathout, A.S. Geneidi, S. Mansour, Exploring the use of nanocarrier systems to deliver the magical molecule; curcumin and its derivatives, J. Controlled Release 225 (2016) 1–30.
[162] H. Mirzaei, A. Shakeri, B. Rashidi, A. Jalili, Z. Banikazemi, A. Sahebkar, Phytosomal curcumin: a review of pharmacokinetic, experimental and clinical studies, Biomed. Pharmacothe. 85 (2017) 102–112.
[163] A.A. Momtazi, A. Sahebkar, Difluorinated curcumin: a promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile, Curr. Pharm. Des. 22 (28) (2016) 4386–4397.