REVIEW

HIF-1α is a Potential Molecular Target for Herbal Medicine to Treat Diseases

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Abstract: HIF-1α is an important factor regulating oxygen balance in mammals, and its expression is closely related to various physiological and pathological conditions of the body. Because HIF-1α plays an important role in the occurrence and development of cancer and other diseases, it has become an enduring research hotspot. At the same time, natural medicines and traditional Chinese medicine compounds have amazing curative effects in various diseases related to HIF-1 subtype due to their unique pharmacological effects and more effective ingredients. Therefore, in this article, we first outline the structure of HIF-1α and the regulation related to its expression, then introduce various diseases closely related to HIF-1α, and finally focus on the regulation of natural medicines and compound Chinese medicines through various pathways. This will help us understand HIF-1α systematically, and use HIF-1α as a target to discover more natural medicines and traditional Chinese medicines that can treat related diseases.
Keywords: HIF-1α, disease, natural medicine, traditional Chinese medicine

Introduction

Mammalian cells depend on oxygen, while hypoxia is also a common physiological and pathological phenomenon in organisms and a common microenvironment for solid tumors.[1] Therefore, the mechanism in the body that can adapt to hypoxia is particularly important to the survival of human beings. Hypoxia-inducible factors (HIFs), a family of transcription factors involved in hypoxia response, is one of the key regulatory mechanisms of hypoxia stress at the cellular level.[2,3] Although there are many mechanisms for hypoxic adaptation in mammals, including those with a faster response time than the HIF system, the HIF system's unique extent of the effects makes it to be a more important regulator of hypoxic responses.[4] Among them, HIF-1α is the most important regulator of oxygen balance in mammals.

HIF-1α, widely existed in mammalian cells, participates in multiple signaling pathways and is a transduction center that mediates hypoxia signals. Increasing studies have found that HIF-1α is closely related to the formation of animal cardiovascular system, the development of cartilage system, the formation of neural embryos and so on. HIF-1α regulated target gene involves erythropoiesis, angiogenesis, cell proliferation, metabolism and apoptosis. For example, HIF-1α can regulate the metabolism, apoptosis and autophagy of tumor cell to suppress tumor cells survival.[5–7] In addition, the new blood vessels generation, epithelial–mesenchymal transition (EMT), transfer invasion, radiation and chemotherapy resistance, pH steady-state of cells are also related to HIF-1α.[8–11] Therefore, HIF-1α is closely related to a variety of physiological and pathological processes in humans.

Abnormally increased or decreased of HIF-1α may cause damage to the body. Up to now, many active ingredients of traditional Chinese medicine (TCM) and natural products have been found to regulate HIF-1α content. For example, curcumin, mainly extracted from Curcumae longae Rhizoma, can inhibit the transcription of HIF-1α in vitro, and then produce a certain therapeutic effect on liver cancer.[12] Traditional Chinese formulas, such as Wenshen Yangxue Decoction, can promote endometrial repair by increasing HIF-1α.[13] Natural medicines that can influence HIF-1α are rich in variety and resources, and they are worthy of development and utilization.

The Protein Structure and Regulation of HIF-1α
HIF-1α Protein Structure

HIF-1α is a 120–130 kD protein. It is the most widely expressed HIF-α subunit in mammalian tissues and is also highly conserved in many other species. The N-terminal of HIF-1α subunits contains basic helix-loop-helix (bHLH) domains, Per-ARNT-Sim-A (PAS-A) and Per-ARNT-Sim-B (PAS-B) domains. The bHLH domain defines a large superfamily of dimeric eukaryotic transcription factors, mediates combination of HIF-1α and DNA.[14] The bHLH domain can be dimerized with the PAS domain to form bHLH-PAS proteins, which are only found in multicellular animals and are a relatively small family of bHLH proteins.[15] The bHLH-PAS domains mediate α, β-dimerization of HIFs and binding of HIFs to hypoxic response elements (HRE) on target genes.[4] The C-terminal of HIF-1α subunits contain oxygen-dependent degradation domains (ODD) and two transcriptional activation domains (TAD), N-TAD and C-TAD (N/C terminal activation domains). In the ODD, the LAPYIXMD motif plays a key role in the binding of HIF-1α to von Hippel-Lindau E3 ubiquitin ligase complex (pVHL), while N-TAD contributes to HIF-1α stabilization against proteasomal degradation, and the C-TAD has the role of recruiting coactivator proteins, CREB-binding protein (CBP)/p300, to form active transcriptional complexes on DNA (Figure 1).[16–18]

The Regulation of HIF-1α
The Synthesis of HIF-1α

The synthesis of HIF-1α under normoxic conditions is regulated by phosphatidyl inositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. The PI3K pathway can mediate the translation of HIF-1α through protein kinase B (Akt) and mammalian target of rapamycin (mTOR), while the MAPK pathway can initiate the translation of HIF-1α through extracellular regulated protein kinases (ERK). mTOR and ERK can activate the translation of specific mRNA sequences by inactivating the inhibitor eukaryotic initiation factor 4E-binding protein (4E-BP) or activating ribosomal protein S6 kinase (S6K).[19,20]

Eukaryotic initiation factor 4E (eIF4E) is a cap-binding protein that can be combined with eIF4G and eIF4A to form eukaryotic initiation factor 4F (eIF4F), which binds to the 5′ cap structure of mRNA to initiate HIF-1α translation. It is generally believed that eIF4E plays a central role in the initial stage of cap-dependent translation since its minimum content and is present in the cell in limiting molar amounts.[21,22] The combination of 4E-BP and eIF4E inhibited the formation of eIF4F. Low phosphorylated 4E-BP has a high affinity with eIF4E and can compete with eIF4G for the binding site of eIF4E, thus preventing the formation of eIF4F and the initiation of
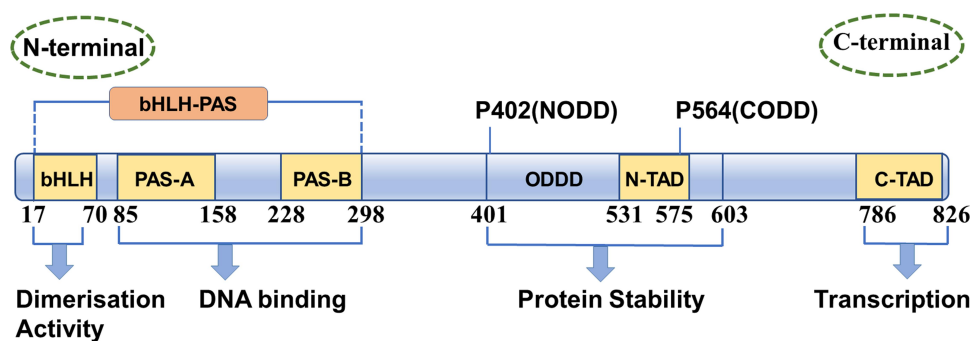

Figure 1 Functional domains in HIF-1α transcription factors. HIF-1α contains a bHLH (basic helix-loop-helix) motif, two PAS (Per-ARNT-Sim) domains (PAS-A and PAS-B) and a C-terminal transcriptional activation domain (C-TAD), a second transcriptional activation domain (N-TAD), as well as N- and C-terminal oxygen-dependent degradation domains (NODD and CODD, respectively).

HIF-1α translation. When 4E-BP is fully phosphorylated, eIF4E is released and can be combined with eIF4G and eIF4A to form eIF4F, which improves the efficiency of translation.[23,24] Activation of mTOR and ERK phosphorylates 4E-BP at multiple sites, thereby releasing eIF4E, allowing eIF4F formation and subsequent cap-dependent translation. What is more, MAPK pathways can also activate the MAPK signal integrating kinase (MNK), which plays a role of eIF4E kinase, so as to promote the formation of eIF4F (Figure 2).[25]

The HIF-1α translation mechanism that S6K mediated is still controversial, but the viewpoint that activation of S6K can increase HIF-1α translation is widely accepted. At first, it was speculated that S6K could stimulate HIF-1α translation by increasing the affinity of ribosomes for the 5′-terminal oligopyrimidine tract (5′ TOP) motif in certain mRNAs.[26] But the new study found that the 5′ TOP motif was not present in HIF-1α mRNA. Furthermore, S6K is dispensable for the translational activation of TOP mRNAs by growth factors.[27] Therefore, the mechanism remains to be further studied.

Although the synthesis of most proteins declines under hypoxia, the translation of a few protein critical to cell survival does not stop, including HIF-1α. However, it is unclear that how HIF-1α is selectively translated during periods of global translation inhibition remains incompletely understood. One possible mechanism is related to the internal-ribosome-entry-site (IRES). IRES do not require the presence of the eIF4F cap-binding complex to initiate translation. It is a short RNA sequence (150~250bp) located at the 5′ untranslated region (UTR) of HIF-1α. IRES can fold into a structure similar to the initiation tRNA, which then mediates the binding of ribosomes to HIF-1α mRNA and initiates its translation in a cap-independent manner.[28–30] However, whether an IRES-dependent mechanism occupies a dominant position in hypoxia conditions is debatable. When researchers evaluated IRES-mediated HIF-1α translation under hypoxia, they found that only <1% of the transcriptional activity was mediated by IRES, suggesting that the role of IRES was not primary.[31] Another mechanism is related to the RNA-binding proteins polypyrimidine tract-binding protein (PTB) and HuR. It was found that in the COCl2-induced hypoxia model, PTB and HuR could combine with the 3′ UTR and 5′ UTR of HIF-1α to jointly promote the translation of HIF-1α.[30,32]

The role of microRNAs (miRNAs) in regulating HIF-1α translation has also received increasing attention. MiRNAs are small endogenous non-coding RNAs consisting of 21 to 25 nucleotides. These miRNAs can be base-paired with the 3′ UTR of mRNA. After forming an RNA-induced silencing complex (RISC), it can degrade the mRNA or hinder its translation.[33] Currently, it has been found that miRNA-17-92 clusters, −155, −199 and −519c can be directly base-paired with HIF-1α mRNA to inhibit translation. MiRNA-21 can indirectly enhance the expression of HIF-1α, mainly by targeting the phosphatase and tension homolog (PTEN) to reduce HIF-1α expression.
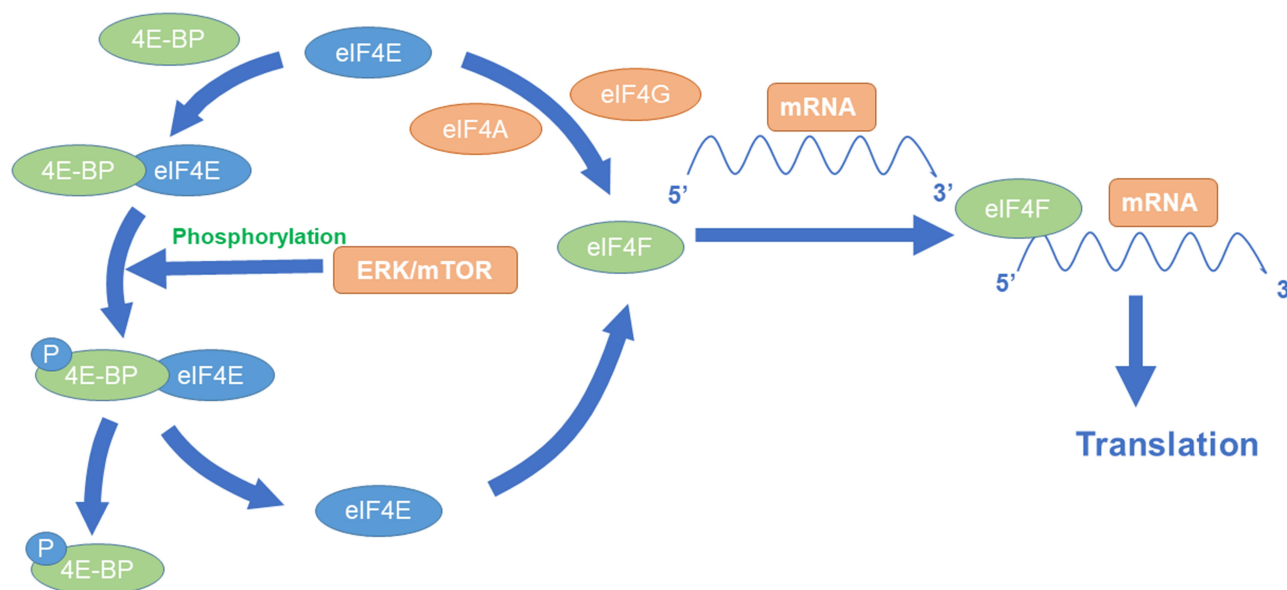

Figure 2 MTOR-mediated synthesis of HIF-1α.

Moreover, the reduction of PTEN can activate AKT and ERK, thereby increasing the expression of HIF-1α.[34]

Degradation and Stabilization of HIF-1α

Located in the cytoplasm, HIF-1α is easily degraded under normal oxygen with a half-life of less than five minutes, but its stability and transcriptional activity are significantly increased under hypoxic conditions.[35–37] HIF-1α regulates its stability mainly through multiple ways.

Prolyl hydroxylase domain proteins (PHD) is an oxygen-dependent enzyme. The oxygen-dependent degradation pathway is called the O_2/PHDs/pVHL pathway (Figure 3). When oxygen levels are normal, it can make two of HIF-1α proline residues (P402 and P564 of HIF-1α) in the ODD (NODD and CODD, respectively) hydroxylation, with oxygen, α-Ketoglutaric acid as substrate, Fe^{2+} and ascorbate as coenzyme. And then pVHL combined with HIF-1α, recruited a variety of ubiquitin protein, to form the E3 ubiquitin ligases proteasome, make HIF-1α subunit ubiquitination, and then degradation by the proteasome.[38–41] PVHL is the substrate recognition component of the complex and can bind directly to HIF-1α. A single hydroxylation at any one site (NODD or CODD) is sufficient for HIF-1α to target the pVHL for degradation.[42] In some cancers, particularly kidney cancer, pVHL is inactivated, and the resultant upregulation of HIF-1α may serve to promote tumor growth.[43] The E3 ubiquitin ligases consist of Elongin-C, Elongin-B and lysine residues catalyzed by pVHL, which degrade HIF-1α by protease. PHD is a key speed limiting enzyme of this pathway. There are 4 PHDs in mammals, namely PHD1-4, among which PHD2 is mainly responsible for regulating the degradation of HIF-1α. PHDs are expressed differently in different tissues and have different affinities with different HIF proteins, which may lead to the diversity of hypoxic responses.[44] Under hypoxic conditions, intracellular accumulation of succinic acid, fumaric acid, reactive oxygen species (ROS) and other chemicals such as CoCl2, dimethyloxalylglycine (DMOG) and iron ion chelator can inhibit the hydroxylation activity of PHD, thereby blocking the O_2/PHDs/pVHL degradation pathway and stabilizing HIF-1α. Among them, DMOG is a structural analogue of α-ketoglutaric acid and a competitive inhibitor of PHD.[45] PHD's catalytic center contains Fe2+, so iron chelators can also inhibit its activity.

The oxygen-dependent O_2/PHDs/pVHL pathway is not the only pathway that leads to the degradation of HIF-1α. There are also some proteins that can affect the stability of HIF-1α. The most typical ones are small ubiquitin-like modifier (SUMO), receptor for activated protein C kinase 1 (RACK1), heat shock protein 90 (HSP90) and proteins related to the PI3K/Akt signaling pathway. SUMOs are small proteins (12 kD) with low sequence identity to ubiquitin, but their 3D structures are very similar. It can bind substrate proteins and carry on the modification after translation, the process is called the SUMOylation.[46] Initially, it was found that SUMO-l can cause SUMOylation of HIF-1α. Overexpression of SUMO-1 under normal and hypoxia can increase the stability and transcriptional activity of HIF-1α, because SUMOylation may compete with ubiquitination for the same modification site of HIF-1α. But new evidence suggests that SUMOylation of HIF-1α can also lead to degradation. Hypoxia induces SUMOylation of HIF-1α, which promotes its binding to the β-subunit of pVHL to form an oxygen-independent HIF-1α-pVHL-E3 ubiquitin ligases
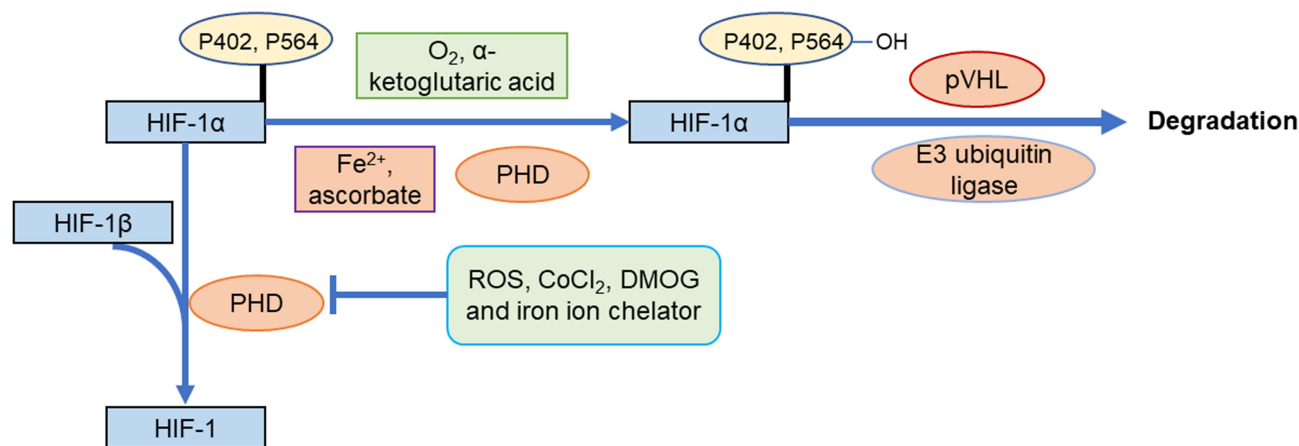

Figure 3 Degradation pathway of HIF-1α by O2/PHDs/pVHL.

complex, and result in ubiquitination and degradation of HIF-1α.[47] Therefore, when PHD is absent, pVHL can also bind to HIF-1α through this pathway. The effect of SUMO on HIF-1α is controversial and needs further research. In addition, the RACK1 and HSP90 can also regulate the stability of HIF-1α in a manner similar to pVHL pathway. After the homodimerization of RACK1, it can bind to the PAS region of HIF-1α, and then recruit Elongin-C and other components of the E3 ubiquitin ligase, resulting in ubiquitination and degradation of HIF-1α. HSP90 can compete with RACK1 to bind to the PAS region of HIF-1α, preventing the ubiquitination of HIF-1α.[48]

The PI3K/Akt signaling pathway is not only involved in the synthesis of HIF-1α but also can regulate the degradation of HIF-1α through different mechanisms. One mechanism is mediated by glycogen synthase kinase-3 (GSK-3). GSK-3 exists in two forms: serine-9 (Ser-9) phosphorylation and tyrosine-216 (Tyr-216) phosphorylation, while Ser-9 phosphorylation is its inactive form, and Tyr-216 phosphorylation is its active form.[49] Active GSK-3 can phosphorylate serine 551 (Ser551), threonine 555 (Thr555), and serine 589 (Ser589) at HIF-1α. After that, HIF-1α is ubiquitinated and degraded. Transient hypoxia can activate the PI3K-Akt pathway, which can make GSK-3 exist in an inactive Ser-9 phosphorylated form, thereby preventing the degradation of HIF-1α. In contrast, chronic hypoxia can inhibit the PI3K/Akt pathway, which can reduce the phosphorylation of Ser-9 and increase the phosphorylation of Try-216. So that more GSK-3 exist in active form which induces degradation of HIF-1α.[50] Another mechanism is achieved by fork-headed box O4 (FOXO4). PI3K-Akt can phosphorylate FOXO4 and prevent it from entering the nucleus, and FOXO4 can induce the ubiquitination and degradation of HIF-1α.[51]

In summary, the degradation of HIF-1α is very complicated, including many pathways and regulators, some of which have not been fully proven and require further research.

Nuclear Transport of HIF-1α

The amount of protein accumulated in the nucleus depends on the relative proportion of its nuclear import and export. Classical HIF-1α nuclear import is mediated by nuclear transport receptors importin. Importin is a receptor of nuclear localization signal (NLS), which can bind to NLS and help nuclear proteins enter the nucleus. HIF-1α in the cytoplasm can enter the nucleus just because its C-terminal NLS (CNLS) can bind to importin α/β, while

N-terminal NLS (NNLS) does not have this function.[52] Moreover, subsequent research found that in addition to the classical importin α/β NLS receptor, importins 4 and 7 can also mediate nuclear import of HIF-1α. They can bind directly to HIF-1α and promote its entry into the nucleus. The difference between the two pathways is that importin a/β may release HIF-1α around the inner nuclear envelope, while importins 4 and 7 release HIF-1α in the nucleus.[53,54]

The nuclear export of HIF-1α involves the MAPK pathway. At first, some scholars found that the HIF-1α protein always appeared on the SDS-PAGE gel as a band with a molecular weight of 20 kDa more than expected. Subsequently, it was found that phosphorylation can change the migration rate of HIF-1α on the gel under normal or hypoxic conditions. Besides, it was confirmed that MAPK played a major role in this change. It can phosphorylate HIF-1α in vivo and in vitro and increase its transcriptional activity. In most research, MAPK does not change HIF-1α protein expression, stability and DNA-binding activity, but promotes HIF-1α transcriptional activity. MAPK increases HIF-1α transcriptional activity through different mechanisms, one of which involves the nuclear export of HIF-1α. The main component of HIF-1α nuclear export is located at the C-terminal nuclear export signal (NES) of HIF-1α, which is an atypical hydrophobic nuclear exporting factor I (CRM1)-dependent signal. HIF-1α in the nucleus can bind to CRM1 through its NES, allowing it to be exported from the nucleus. But when the Ser641 or Ser643 adjacent to NES is phosphorylated by MAPK, NES will be masked and unable to bind to CRMI, so that phosphorylated HIF-1α is accumulated in the nucleus[55,56] (Figure 4).

Heterodimerization, Transcriptional Activation of HIF-1α and Interaction with Other Proteins

The stabilization and nuclear transport of HIF-1α are essential for its function, but these are not enough. Phosphorylated HIF-1α must be heterodimerized with HIF-1β to form HIF-1. After its active regions N-TAD and C-TAD bind to co-activating factors such as P300/CBP (CREB-binding protein), an active complex is formed. The complex then binds to the HRE on the target gene to exerting its activity.

Under normoxic conditions, the N-terminal of aspartic acid hydroxylase (also known as factor-inhibiting HIF-1α, FIH) can bind to the HIF-1α region, while the C-terminal cannot bind to HIF-1α. What is more, FIH-1 can
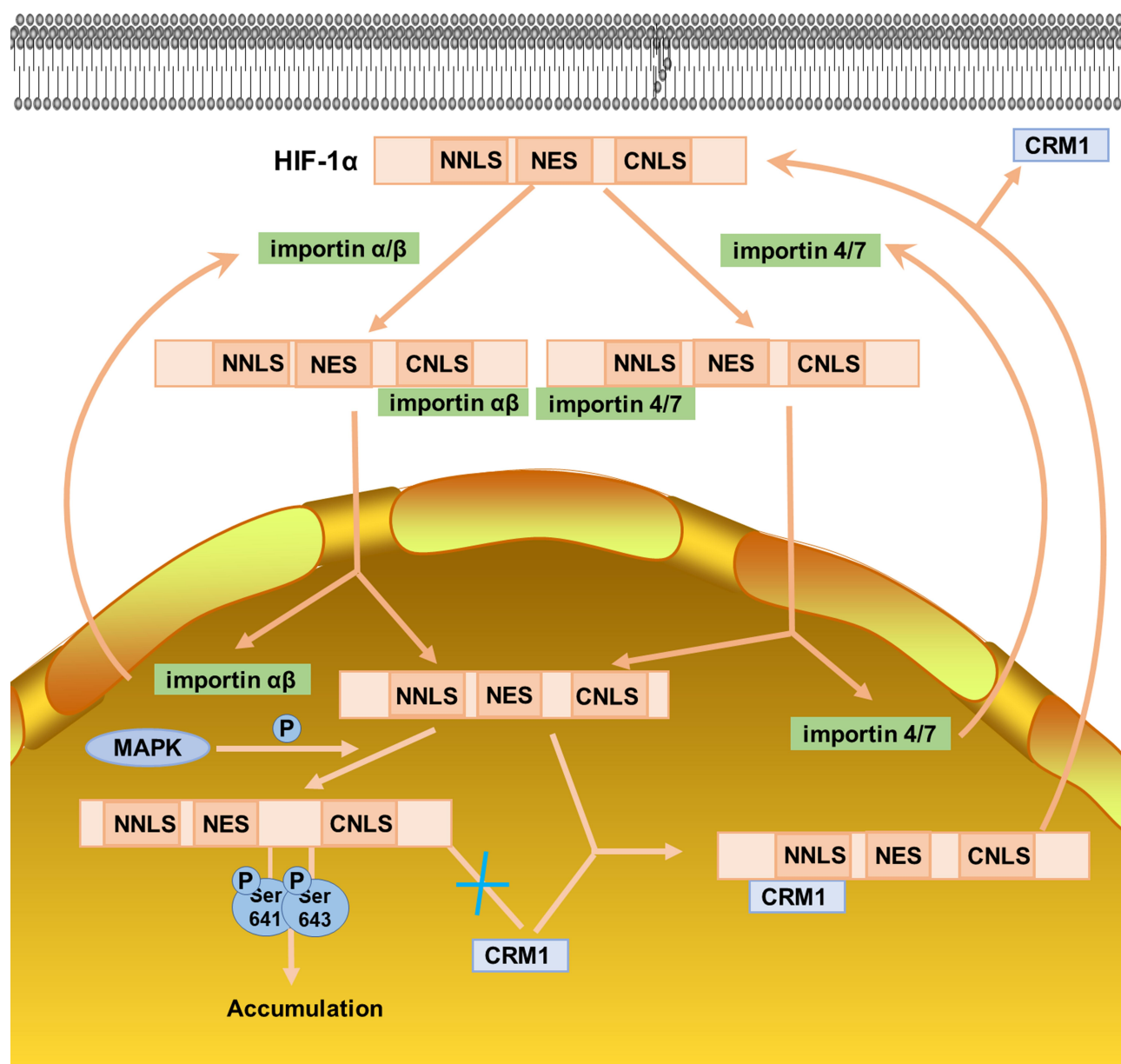
Figure 4 Nuclear transport of HIF-1α.

hydroxylate Asn803 in the C-TAD domain of HIF-1α subunit, blocking the binding of HIF-1α to p300/CBP, thereby inhibiting the transcriptional activation of HIF-1. Like PHDs, FIH-1 is inhibited when in the hypoxia or the presence of $CoCl_2$, DMOG, Fe^{2+}, etc., and HIF-1α subunits that have not been hydroxylated were successfully combined with p300/CBP, thus activating target gene transcription (Figure 5).[57] FIH-1 and PHDs have different requirements for oxygen to maintain the activity. In vitro, the Km of FIH for O_2 was about 40% of its atmospheric concentration, being about one-third of those of the PHDs.[58] Therefore, PHDs can be inactivated under mild

hypoxia (1% −5% O_2), while FIH-1 can be inactivated only under severe hypoxia. In addition, researchers have found that pVHL can also regulate FIH-1, and FIH-1 can bind to the β-domain of pVHL.[59] In aerobic conditions, Asn803 in C-TAD of HIF-1α is hydroxylated by FIH-1, and the combination of pVHL and FIH-1 can enhance this effect. In moderate hypoxia conditions, PHDs become inactive, which causes the accumulation of HIF-1α. Moreover, the FIH-pVHL complex depolymerized, and it can weaken the binding of FIH-I to C-TAD, thereby partially activating C-TAD. On the other hand, when in severe hypoxic conditions, FIH-1 and PHDs were completely
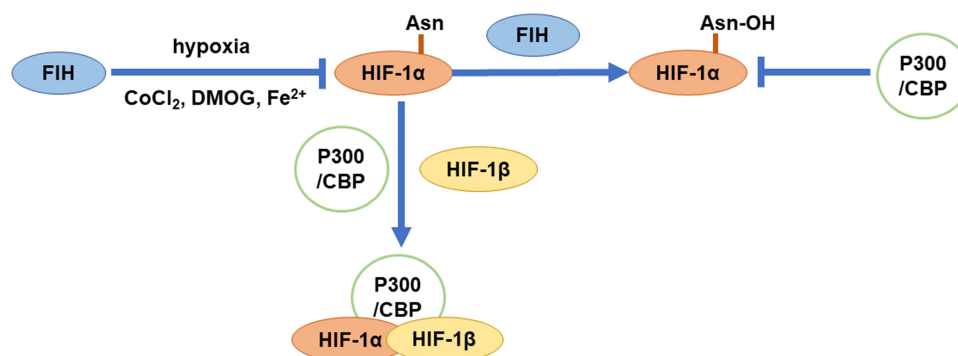
Figure 5 Transcriptional activation of HIF-1α.

inactivated, so C-TAD is fully activated. This makes us speculate that when the oxygen concentration begins to decrease, the cells first express a series of genes regulated by N-TAD, and when the oxygen concentration is further lower, the genes regulated by C-TAD can be expressed.[60]

Previous studies suggested that only C-TAD needs to recruit the transcription co-activator p300/CBP, so that C-TAD can play its role. However, the subsequent research found that N-TAD mediated transcriptional activities also require the participation of CBP. The difference is that C-TAD is bound to the CH1 region of CBP, while N-TAD is bound to its CH3 region.[61] Moreover, MAPK can increase the recruitment of P300/CBP to HIF-1α, because P300 and CBP are direct phosphorylation substrates of MAPK, and MAPK can cause phosphorylation of P300 and CBP. This phosphorylation can have specific effects on the affinity of P300/CBP and different protein factors, resulting in the redistribution of P300/CBP in the complex of interacting factors. In particular, because MAPK signals can stimulate the transcriptional activity of P300/CBP, so it is likely to increase the interaction between P300/CBP and basic transcriptional mechanisms.[62] In addition to MAPK, the PI3K/Akt pathway can also indirectly regulate the binding of HIF-1α to p300/CBP. PI3K/Akt can phosphorylate fork-head box O3a (FOXO3a), thereby preventing FOXO3a from entering the nucleus. FOXO3a can interfere with the recruitment of p300 to HIF-1α after entering the nucleus, thereby negatively regulating its transcriptional activation activity.[63]

Role of HIF-1α in Different Physiological or Pathological States
HIF-1α and Angiogenesis
Angiogenesis is one of the basic events of many physiological processes (eg, embryonic development, and menstrual cycle) and pathological processes (eg, tumor, ischemic disease, chronic inflammation, diabetic retinopathy, endometrial hyperplasia, psoriasis, obesity, and wound healing). HIF-1α plays an important role in ischemia-induced angiogenesis by upregulating gene expression of proteins associated with the vascular system, while the most typical of which is vascular endothelial growth factor (VEGF) and its receptor. HIF-1α can regulate the angiogenic factor angiopoietin-1, angiopoietin-2, placental growth factor (PLGF), platelet-derived growth factor B (PDGF-B) and VEGF, to participate in the whole process of angiogenesis.[64] Related studies have confirmed that removing HIF-1α gene or blocking HIF-1α transcription can prevent tumor cells from secreting VEGF and inhibit the formation of tumor neovascularization. With the continuous growth and volume increase of the tumor, hypoxic necrosis occurred due to insufficient blood supply, which induced the overexpression of HIF-1α. Meanwhile, HIF-1α can enhance the expression of its downstream target gene VEGF, and then act on VEGF-R1 and VEGF-R2 on the surface of vascular endothelial cells, thereby promoting angiogenesis and accelerating tumor metastasis.[65] In the femoral artery ligation model with HIF-1α gene knock-out, it was found that vascular growth factors such as VEGF were not activated and the reperfusion capacity decreased after ischemia.[66] In addition, HIF-1α also had a role in promoting angiogenesis in models of myocardial hypertrophy, myocardial infarction, wound healing and retinal angiogenesis.[67–69]

HIF-1α and Cancer
The rapid proliferation of tumor cells leads to insufficient blood supply, so that tumor cells are often in a hypoxic environment. A large number of literatures have reported that HIF-1α is overexpressed in breast cancer, ovarian

cancer, esophageal cancer, colon cancer, lung cancer and other tumor tissues. In addition, HIF-1α expression was significantly higher in multiple metastatic tumors than in primary tumors.[70–73] Current studies have found that HIF-1α is involved in transcriptional regulation of more than 70 target genes in various tumor growth processes. Among them, there are four types of gene that are closely related to tumor, which are factors related to glucose transport and glycolysis, factors related to angiogenesis, factors related to tumor proliferation and apoptosis, and factors related to tumor invasion and metastasis.[74] They induce a series of responses in cells and tissues to adapt to the hypoxic environment, promoting tumor angiogenesis, and also increasing the invasiveness of the tumor itself and its resistance to chemoradiotherapy.

In tumor cells, HIF-1α can not only promote angiogenesis but also help tumor cells obtain energy by reconstructing the metabolic pathway of cells, among which glycolysis is an important means. First, HIF-1α is able to initiate glucose transporter and lactate dehydrogenase A (LDHA) to mediate pathway conversion to non-oxidative carbon metabolism and ATP-producing pathways such as glycolysis. In addition, PDK protein encoded by pyruvate dehydrogenase kinase-1 (PDK1), another HIF-1α target gene, inhibits the production of acetyl CoA, blocks the tricarboxylic acid cycle, and reduces oxygen consumption. It was found that cells lacking HIF-1α reduced ATP production under hypoxic conditions, producing more oxygen-free radicals and promoting apoptosis.[75] In addition to these two pathways, activation of HIF-1α affects the pentose phosphate pathway, which converts the intermediate products of glycolysis into 5-phosphoribose, an important raw material for synthesis of nucleotides.[76] These results suggest that HIF-1α promotes cell survival under hypoxic conditions by reconstructing cell metabolic pathways, one of the steps required to convert glucose metabolism into RNA and DNA synthesis, which is important for survival and growth of hypoxic tumor cells.

HIF-1α can also promote the proliferation of tumor cells through the regulation of related factors. For example, HIF-1 can induce the production of factors such as insulin-like growth factor-2 (IGF-2) and transforming factor-2 (TGF-2). These factors activate the MAPK and PI3K pathways through binding to cognate receptors, which not only cause cells hyperplasia but also increase the activity of HIF-1α and accelerate the transcriptional activity of HIF-1α-induced genes. This activity plays an important role in the evolution of tumors.[77] In terms of tumor cell

apoptosis, the mechanism is more complex. First, many scholars believed that HIF-1α could promote the apoptosis of tumor cells. HIF-1α stabilized p53 by inhibiting p53 ubiquitination and blocking p53 translocation outside the nucleus, thus inducing various apoptotic genes to promote apoptosis.[78] In other studies, HIF-1α also had an anti-apoptotic effect. Hypoxia or COCl2 can induce the expression of HIF-1α and inhibit the apoptosis of hepatoma cell line HepG2 caused by tert-butyl hydrogen peroxide or serum depletion.[79]

In addition to the above aspects, HIF-1α can also enhance the invasion and metastasis of tumor, which are closely related to the matrix metallo-proteinases (MMPs). HIF-1α may increase the expression of MMPs, thus promoting the metastasis of malignant tumors. On the other hand, increased HIF-1α lead to the decreased of epithelial cadherin (E-cad) and β-catenin (β-cat), and the destruction of the E-cad/β-cat complex can reduce the adhesion between cells and matrix, which finally cause cell separation and migration. Further studies also found that multidrug resistance gene 1 (MDR1) and its encoded p-glycoprotein could be increased by HIF-1α, and the high expression of both was one of the main mechanisms of drug resistance in tumors.[80,81]

HIF-1α and Inflammation

HIF-1α can be detected in inflammatory diseases such as immune inflammation, bacterial infection, macrophage metabolism and viral infection. When an inflammatory response occurs, increased vascular permeability will cause more immune cells to reach the site of inflammation. At the same time, the increased oxygen consumption of inflammatory cells and antigens will lead to the formation of a local hypoxic environment in the inflammatory site due to the slow blood flow, which will induce the immune cells to transcribe HIF-1α.[82] The response of immune cells to hypoxia is closely related to the nuclear factor-κb (NF-κb). As a key immune regulator, NF-κb can positively regulate the transcription of HIF-1α mRNA under hypoxia, and it can also activate NF-κb in macrophages, neutrophils, and some non-immune cells, which are not only participants in acute and chronic inflammation but also crucial front-line effectors for innate host defense against invading microbial pathogens. Hypoxia inhibits PHD1 activity and makes HIF-1α accumulation, leading to the activation of inhibitor of NF-κb (Iκb) kinase (IKK), which then phosphorylates NF-κb. Dissociated NF-κb

activates transcription of corresponding downstream genes, such as inflammatory cytokines.[83]

HIF-1α plays an important role in the inflammatory response. It can not only promote the secretion of inflammatory factors but also be regulated by inflammatory factors. Take rheumatoid arthritis (RA), a chronic, autoimmune inflammatory disease characterized by synovial inflammation in the joints, especially the hands and feet, and progressive destruction of these and other joints. IL-1 and TNF-α play important roles in the progression of RA as pro-inflammatory and immune regulators. Stimulated by IL-1 and TNF-α, fibroblast synovial cells in RA patients can promote HIF-1α increase in mRNA and protein levels. Among them, IL-1 can increase the binding of the heterodimer HIF-1 to the HIF consensus sequence.[84,85] In addition, IL-33 also can promote the expression of HIF-1α in synovial tissue of RA. The study found that the level of IL-33 in the synovial fluid of RA patients was increased, and the expression of HIF-1α upregulated, while the expression of HIF-1α, in turn, could control the expression of IL-33 through the p38 and ERK pathways, thus forming a closed loop of HIF-1α/IL-33, and aggravating the inflammatory response.[86] Meanwhile, the role of VEGF, another downstream target gene of HIF-1α, cannot be ignored in RA. The synovial membrane of RA patients can produce a large amount of HIF-1α, which further stimulates the production of VEGF. During the development of RA, VEGF can promote the formation of new blood vessels in synovium and further aggravate synovial tissue hyperplasia.[87]

HIF-1α and Physiological Hypoxia

In addition to pathological hypoxia, HIF-1α also plays an important role in the physiological hypoxia of the body. After entering plateau or strenuous exercise, hematopoietic organs increase the oxygen-carrying capacity of the blood by increasing the number of red blood cells, a process mediated by erythropoietin (EPO), the target gene of HIF-1α. EPO is an erythrocyte-specific hematopoietic hormone produced mainly by the kidney and liver. The presence of EPO promotes the production of hemoglobin and red blood cells and is a key factor in regulating the body's balance in response to hypoxia. When the body is stimulated by hypoxia, the activated HIF-1α binds to the HRE located in the promoter region of the EPO gene, which then triggers the transcription of the EPO gene.[88,89] Familial polycythemia is a genetic disorder characterized by an abnormal increase in hemoglobin and red blood cells, which has

been shown to be caused by a mutation in VHL that prevents HIF-1α from hypoxia and activates EPO.[90,91] In the adaptation of plateau and sea level mice to hypoxia, hypoxia-activated HIF-1α expression in sea level mice but had no significant effect on HIF-1α expression in plateau mice for generations. It means that the adaptive strategies of highland mammals to hypoxia seem to differ genetically from those of lowland mammals by a long evolutionally acclimatization to the hypoxic environment.[92]

Bioactive Components of Natural Medicine or Traditional Chinese Medicine Prescription

Natural medicines and TCM formulas have multi-target and multi-level therapeutic effects on various diseases due to their various components. After a large number of studies on their active components, they can be roughly divided into flavonoids, quinones, terpenes, polysaccharides and glycosides, etc., based on the chemical structure differences. As a central regulator, HIF-1α is involved in many diseases. On the one hand, overexpression of HIF-1α is closely related to diseases such as solid tumors, and on the other hand, inhibition of HIF-1α is involved in hypoxic-ischemic diseases such as anemia. Therefore, by inhibiting or promoting HIF-1α, it can play a therapeutic role in related diseases. Natural medicine and TCM formulas can affect the content of HIF-1α in the body by regulating the synthesis, degradation and nuclear transport of HIF-1α, thereby playing a therapeutic effect on cancer, inflammation and other diseases.

Inhibition of HIF-1α
Bioactive Components
The pathogenesis of many diseases such as solid tumor, endometriosis, renal interstitial fibrosis and intestinal epithelial barrier dysfunction is closely related to the overexpression of HIF-1α, which threatens human health.[93–96] Up to now, researchers have found that they can mainly downregulate HIF-1α in the following ways: 1) block HIF-1α/p300 interactions; 2) decrease the expression of HIF-1α mRNA; 3) reduce stability of HIF-1α protein (Figure 6).[97] In modern research, a variety of natural medicines and traditional Chinese medicine prescriptions can achieve a therapeutic effect by reducing the content of HIF-1α. However, it is regrettable that the pathway through which many natural medicines or traditional Chinese medicine
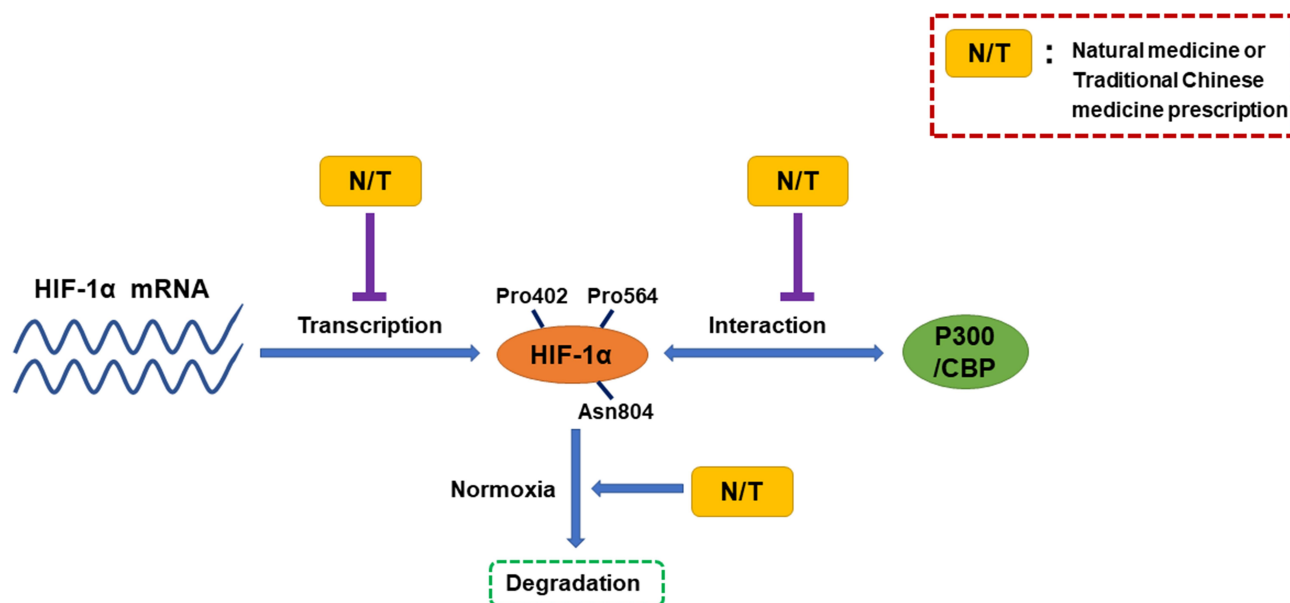
Figure 6 Natural medicines and traditional Chinese medicine prescriptions can mainly downregulate HIF-1α in three following ways.

prescriptions reduce HIF-1α is unknown, and further research is needed.

The known TCMs, such as Curcumae longae Rhizoma (named "Jianghuang" in Chinese), Curcumae Radix (named "Yujin" in Chinese), Curcumae Rhizoma (named "Ezhu" in Chinese), have the effects of promoting blood circulation and promoting *qi*. In modern pharmacological studies, researchers have found that in addition to the above-mentioned effects, they can also exert anti-inflammatory and anti-tumor effects, all of which are attributed to the curcumin, an active ingredient in these TCMs mentioned above. Curcumin is a diketone compound which is widely used in food industry as a spice and colorant because of its unique aroma and color. In addition, continuous evidences show that anti-inflammatory and anti-tumor efficacy of curcumin is closely related to its inhibitory effect on HIF-1α.[98] Curcumin has therapeutic effects on a variety of cancers, in particular for the liver cancer. As mentioned above, local hypoxia, increased angiogenesis, and increased cell adhesions are commonly accompanied by tumors in the body, and interestingly curcumin has a significant effect on these phenomena. First, in the hypoxia-induced HepG2 liver cancer cell model, after co-incubation with curcumin, the transcriptional activity of HIF-1α is inhibited, which in turn reduce the produced HIF-1α. At the same time, in vascular endothelial cells, the expression of HIF-1α and its downstream target gene VEGF will also decrease, inhibiting angiogenesis.[12] In thyroid cancer, researchers further found that curcumin can inhibit the mRNA and protein expressions of HIF-1α by reducing the DNA-binding potential of HIF-1α to hypoxia response element under hypoxic conditions. In addition, after co-incubating with K1 papillary thyroid cancer cells, the expression of E-cadherin increased and the activity of metalloproteinase-9 (MMP-9) enzymes decreased. All the above results indicated that curcumin had a strong anti-metastatic effect and could prevent the malignant metastasis of cancer cells.[99] With the continuous in-depth study of curcumin's effects on cancer, researchers have focused their attention on the effect of curcumin on cancer metabolism. After continuous efforts, the researchers were surprised to find that curcumin can also down-regulate pyruvate kinase M2 (PMK2), a key regulator of the Warburg effect, through the mTOR-HIF-1α signaling pathway, and inhibit glucose uptake and lactic acid production in a variety of cancer cell lines.[100] In addition to the effective treatment of cancer, curcumin can also exert anti-inflammatory, anti-apoptotic and anti-oxidant effects by inhibiting HIF-1α, which can be used to treat atherosclerosis, hemophilia and other diseases. First, we take atherosclerosis as an example. Atherosclerosis is characterized by accumulation of lipid and fibrous elements and is accompanied by inflammation and immune response in the vascular endometrium. In response to these phenomena, researchers have found that after treatment with curcumin, the total cholesterol and lipid levels in macrophages induced by hypoxia will decrease to varying degrees. At the same time, the expression of HIF-1α will decrease with the inhibition of the ERK signaling pathway, further

reducing its downstream target genes such as VEGF and PDGF. In this case, VEGF is responsible for the formation of new blood vessels, while PDGF can cause the proliferation and vasoconstriction of vascular smooth muscle cells and aggravate the disease response. Curcumin can also effectively relieve the inflammation and immune response of the vascular intima during the development of atherosclerosis. For example, curcumin also can inhibit the hypoxia-induced the macrophage apoptosis and the upregulated protein level of inflammation factor, IL-6 and TNF-α. Therefore, all these evidences suggest that curcumin could be a potential drug for treating atherosclerosis.[79] Of course, studies have shown that curcumin can also treat hemophilia by inhibiting inflammation and angiogenesis[101] (Figure 7). In addition to inhibiting the above factors, it can also inhibit IL-1 and MMP, other mechanisms are shown in Table 1.[102] In addition to inhibiting the above factors, it can also inhibit IL-1 and MMP, other mechanisms are shown in Table 1.[102] Flavonoids are an important part of natural medicines, and many compounds have the effect of inhibiting HIF-1α. Take isoquercitrin as a simple example. Isoquercitrin is mainly derived from Gossypium herbaceum L. and Apocynum cannabinum Linn. It is a phytoestrogen and a flavonoid. Isoquercitrin has a significant effect on osteoporosis caused by abnormally elevated HIF-1α after menopause. By suppressing NF-κB activation, HIF-1α mRNA levels are reduced, bone histological characteristics are improved, and lumber strength is increased.[103] Apigenin, a flavonoid mainly existing in *Apium graveolens* L., can improve abnormal glucolipid metabolism by reducing the expression of HIF-1α and subsequent up-regulating PPARα-mediated CPT-1 and PDK-4 expressions and down-regulating PPARγ-mediated GPAT and GLUT-4 expressions.[104,105]

In addition to flavonoids, quinones also have inhibitory effect on HIF-1α. Rhei Radix et Rhizoma (named "Dahuang" in Chinese), a known TCM, is mainly used in the treatment of acute intestinal obstruction. Moreover, as a laxative, it has been proven to regulate the contractility of intestinal smooth muscle. However, it has been found in modern studies that the active ingredient emodin, an anthraquinone extracted from Dahuang has the effect of treating intestinal epithelial barrier dysfunction. In the critically ill state, intestinal barrier dysfunction often occurs, involving inflammation and hypoxia damage of intestinal epithelial cells. In certain studies, it has been clearly clarified that NF-κB and HIF-1α signaling pathways will promote the development of this disease. Furthermore, cyclooxygenase (COX) 2 is a key enzyme in the intestinal barrier failure
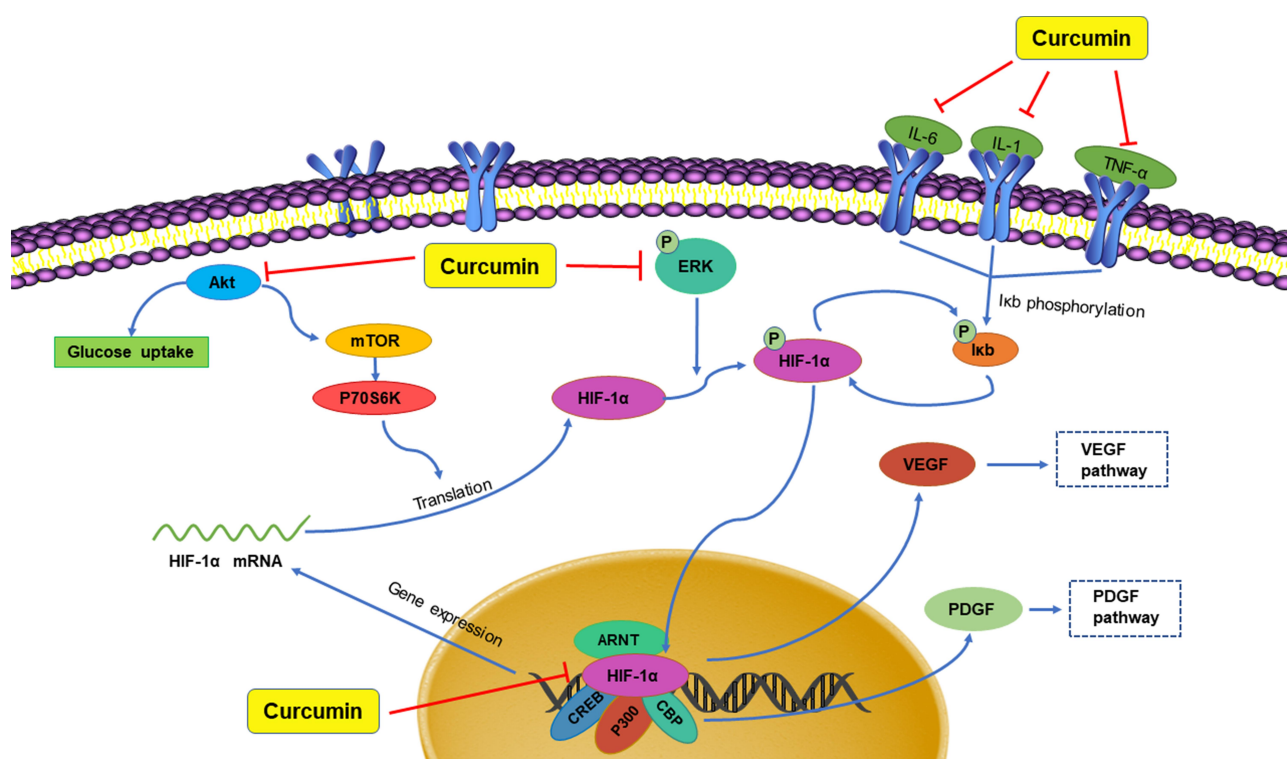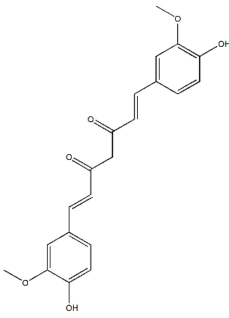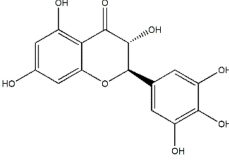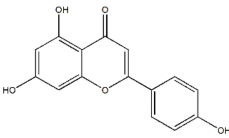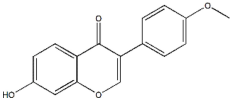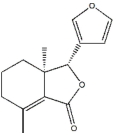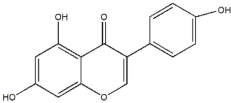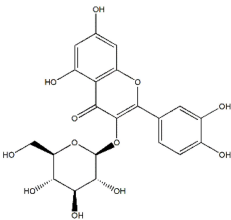

Figure 7 Curcumin downregulates the content of HIF-1α.

Table 1 Bioactive Components of Natural Medicine That Can Inhibit HIF-1α

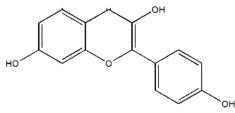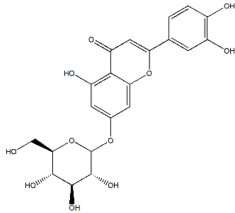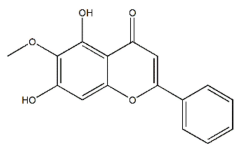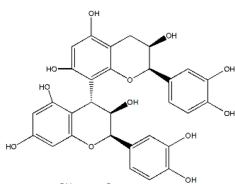| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Flavonoids						
Curcumin	*Curcuma longa* L.; *Curcuma rcenyujin* Y; *Curcuma aeruginosa* Roxb.; *Acorus tatarinowii* Schott		HepG2, HUVECs cells Human THP1 cells Synovial tissue and PB of HA patients	Suppressing the transcriptional activity of HIF-1α and the expression of VEGF, inhibiting angiogenesis; repressing the expression of HIF-1α at the protein level and the downstream genes of HIF-1α, such as HMOX1, ROS, VEGF and PDGF; Suppressing inflammation and angiogenesis by inhibiting HIF-1α, IL-1, IL-6, VEGF and MMPs.	Liver cancer Atherosclerosis Hemophilic arthropathy	[12,79,102]
			K1 PTC cells	Repressing HIF-1α expression, hypoxia-induced ROS generation, and the DNA-binding potential of HIF-1α to hypoxia response element under hypoxic conditions, up-regulating E-cadherin expression and inhibiting MMP-9 enzyme activity.	Thyroid cancer.	[99]
			H1299, HEK293, PC3, HeLa and MCF-7 cells.	Decreasing glucose uptake and lactate synthesis by suppressing pyruvate kinase M2 expression via inhibition of mTOR-HIF-1α axis.	Cancers.	[100]
Ampelopsin	*Hovenia dulcis* Thunb.		HUVECs and HepG2 cells	Suppressing both VEGFR2 signaling and HIF-1 α expression, leading to decreased cell proliferation, migration, invasion and tube formation.	Cancer and other angiogenesis-related human diseases.	[122]
Apigenin	*Apium graveolens* L.		H9c2 cells	Reducing the expression of HIF-1α, increasing PPARα-mediated CPT-1 and PDK-4 expressions and decreasing PPARγ-mediated GPAT and GLUT-4 expressions.	Abnormal glucolipid metabolism.	[104,105]
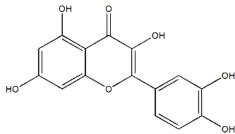
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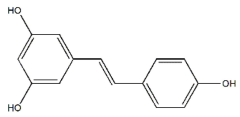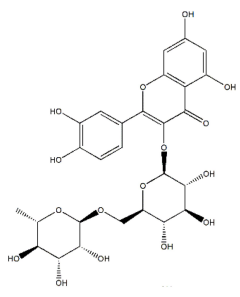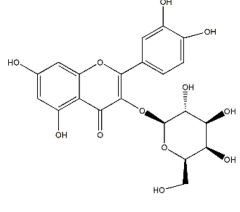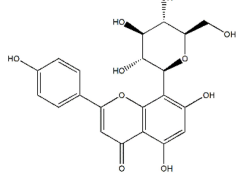| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Formononetin	*Astragalus membranaceus*		Female, Balb/c nude mice inoculated with cervical cancer HeLa cells (aged 6-8 weeks and weighing 15-20 g)	Inhibit the growth of cervical cancer and reducing the mRNA and protein expression levels of HIF-1α and VEGF in mouse cervical cancer.	Cervical cancer.	[123]
Fraxinellone	*Dictamnus dasycarpus* Turcz		A549, HeLa, Hep3B, HUVEC, and HLF-a cells	Inhibiting PD-L1 expression by downregulating the STAT3 and HIF-1α signaling pathways, subsequently inhibiting proliferation and angiogenesis in cancer cells.	Cancers.	[124]
Genistein	*Sophora tonkinensis* Gagnep.		HCC-LM3, SMMC-7721, Hep3B, Bel-7402, and Huh-7 cells.	Abrogating aerobic glycolysis and triggering apoptosis of HCC cell lines by down-regulating HIF-1α and thereby inactivating GLUT1 and HK2 activity.	Hepatocellular carcinoma.	[125]
			BALBc nu/nu mice inoculated with HCC cells.	Reducing tumor size and increasing the apoptotic area by down-regulating HIF-1α/GLUT1/HK2 activity.	Hepatocellular carcinoma.	[125]
			A549 cells.	Inhibiting proliferation and promoting apoptosis by attenuating the expression of HIF-1α through the down-regulation of PI3K/Akt signaling pathways.	Lung cancer.	[126]
Isoquercitrin	*Gossypium herbaceum* L.; *Apocynum cannabinum* L.		Three-month-old female albino rats after bilateral ovariectomy (weighing 150–170 g)	Suppressing NF-κB activation, reducing HIF-1α mRNA levels, improving bone histological characteristics and lumber strength.	Osteoporosis caused by menopause.	[103]

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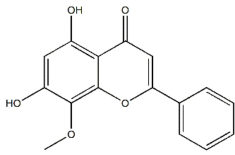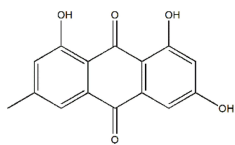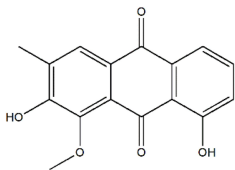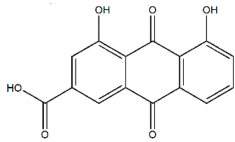| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Kaempferol	*Kaempferia galanga* L.		HUVECs	Suppressing the activation of HIF-1α, VEGFR2, and other markers of ERK/p38 MAPK and PI3K/Akt/mTOR signaling pathways in endothelial cells, inhibiting cell migration and tube formation.	Diseases related to angiogenesis.	[127]
Luteolin	*Dendranthema morifolium* (Ramat.) Tzvelev; *Lonicera japonica* Thunb.; *Lonicera confuse* (Sweet) DC.; *Lonicera hypoglauca* Miq.; *Lonicera fulvotomentosa* Hsu et S. C. Cheng;		H9c2 cells	Inhibiting HIF-1α expression and subsequent modulation of PPARα-mediated target genes, including CPT-1A, PDK-4, and GLUT-4.	Abnormal glucolipid metabolism of hypertrophic myocardial cells.	[128]
Oroxylin A	*Scutellaria baicalensis* Georgi		Human hepatocyte LO₂ cells	Suppressing the nuclear translocation of HIF-1α, reducing the accumulation of lipid droplets associated with regulating the lipid metabolism genes.	Hepatic steatosis.	[129]
Procyanidin B2	Red wine, green and black tea, cocoa/chocolate, and fruit juices.		Six-week-old male C57 mice injected with CCl₄ (weighing 24±2 g), human immortal LX2 cell	Suppressing the expressions of VEGF-A, HIF-1α, α-SMA, Col-1 and TGF-β1 of HSCs in vivo and in vitro, inhibiting the proliferation and inducing apoptosis of HSC.	Liver fibrosis.	[130–132]
Quercetin	Leaves, fruits, and vegetables including green tea, apples, berries, onions, red wine, etc.		LNCaP, CX-1, SkBr3, NCI-H157, HOS and MG63 cells.	Attenuating the synthesis of HIF-1α and its downstream target, VEGF.	Prostate cancer, colon cancer, breast cancer, lung cancer, osteosarcoma.	[133–135]

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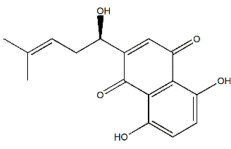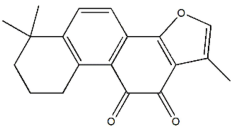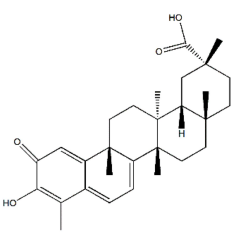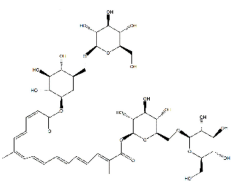| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Resveratrol	Grapes, berries, peanuts, and other plant sources.		The human pancreatic cancer cell lines BxPC-3 and Panc-1.	Decreasing production of ROS, ROS-induced invasion and migration, HIF-1α protein synthesis and expression of metastatic-related factors including uPA and MMP-2 through the activation of a hedgehog signaling pathway.	Pancreatic cancer.	[136]
Rutin	*Ruta graveolens* L.; *Scphora japonica* L.; *Hypericum aseyron* L.; *Berchemia polyphylla Wall*, var *leioclada* Hand – Mazz; *Fagopyrum esculentum Moench*; *Mallotus japonicus Muell - Arg*		GBMs cells lines U251, U87, HS683 and A172 and human normal cell HA	Inhibiting HIF-1α/MMP-2 pathway, inducing apoptosis and reducing the MDA level after radiotherapy	Glioblastomas	[137]
Hyperin	*Eucommia ulmoides Oliv.*		GBMs cells lines U251, U87, HS683 and A172 and human normal cell HA	Inhibiting HIF-1α/MMP-2 pathway, inducing apoptosis and reducing the MDA level after radiotherapy	Glioblastomas	[137]
Vitexin	*Vitex negundo* L. var. *cannabifolia* (Sieb. et Zucc.) Hand-Mazz.		Balb/c nude mice inoculated with SU3 cells (weighing 18-20 g)	Inhibiting HIF-1α protein expression and subsequent decrements of its downstream protein expressions such as VEGF, GLUT-1, GLUT-3, reducing antioxidant capacity.	Glioma.	[138]
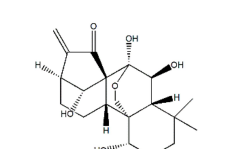
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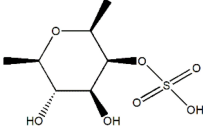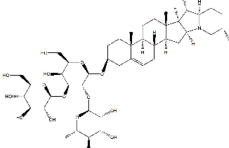| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Wogonin	*Scutellaria baicalensis* Georgi		HCT116 cells;	Decreasing the expression of glycolysis-related proteins (HKII, PDHK1, LDHA), glucose uptake, and lactate generation, down-regulating HIF-1α expression and glycolysis through inhibiting PI3K/Akt signaling pathway.	Cancers	[139]
			Male BALB/c nude mice (35–40 days old and weighing 18–22 g) injected with HCT116 cells.	Inhibiting the growth of transplantable tumors and the expression of HIF-1α, glycolysis-related proteins and PI3K/Akt.	Cancers	[139]
Quinones						
Emodin	*Rheum palmatum* L.		Caco-2 cells; AsPC-1, BxPC-3, HPAF-2, MiaPaCa2, and Panc-1 cells, male athymic Balb/c mice injected with MiaPaC2 cells (4–5 weeks old and weighed 17–20g)	Inhibiting the HIF-1α and NF-κB signaling pathways, increasing zonula occludens-1 (ZO-1) expression in vivo and in vitro. Reducing HIF-1α through its biosynthesis, inhibiting the growth of cancer cells by inhibiting their proliferation.	Intestinal epithelial barrier dysfunction. Cancers.	[104,105]
Obtusifolin	*Cassia tora* L.		ARPE-19 cells	Inhibiting the transcription and translation of HIF-1α, VEGF, VEGFR2 and eNOS, reducing cell viability under hypoxic conditions and arrest cells in G1 phase.	Choroidal neovascularization.	[107]
Rhein	*Rheum palmatum* L.		AsPC-1, BxPC-3, HPAF-2, MiaPaCa2, and Panc-1 cells, male athymic Balb/c mice injected with MiaPaC2 cells (4–5 weeks old and weighed 17–20g)	Reducing HIF-1α through its biosynthesis, inhibiting the growth of cancer cells by inhibiting their proliferation.	Cancers.	[106]
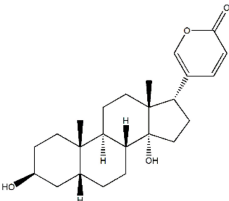
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Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Shikonin	*Arnebia euchroma* (Royle) Johnst.; *Lithospermum erythrorhizon* Sieb. et Zucc.; *Arnebia guttata* Bunge		HMVEC-dLy cells	Inhibiting cord formation ability of lymphatic endothelial cells, decreasing nuclear factor-kappaB (NF-κB) activation by phosphorylation and nuclear translocation of NF-κB p65, and also reducing both mRNA and protein levels of hypoxia-inducible HIF-1α.	Cancers, lymphatic metastasis.	[140]
Tanshinone IIA	*Salvia miltiorrhiza* Bunge		HepG2 cells	Inducing apoptosis, and increasing the expression of p53, inhibiting cell proliferation and expression of HIF-1α and VEGF.	Hepatocellularcarcinoma	[119]
Terpenes						
Celastrol	*Tripterygium wilfordii* Hook f.		HepG2 cells	Inducing apoptosis, inhibiting the expression of PPARβ and HIF-1α, and elevating the expression of p53.	Hepatocellular carcinoma.	[110]
Crocin	*Crocus sativus* L.		Human gastric cancer cell lines AGS and HGC-27 and the normal gastric epithelial cell line GES-1.	Reducing expression of KLF5 and HIF 1α, increasing microRNA-320 expression, inhibiting the migration, invasion, and EMT of gastric cancer cells.	Gastric cancer.	[141]
Oridonin	*Rabdosia rubescens* (Hemsl.) Hara		MDA-MB-231, MCF-10A and HUVECs cells, female BALB/c mice inoculated with 4T1 cells (5–6 weeks old, weighed 14–16 g)	Decreasing expression of E-cadherin, while increasing the expression of N-cadherin, Vimentin, Snail, HIF-1α, VEGF-A and VEGFR2.	Breast cancer.	[111]
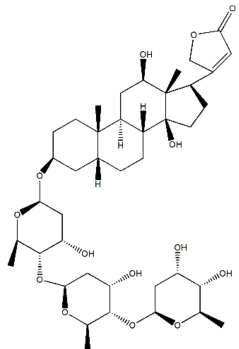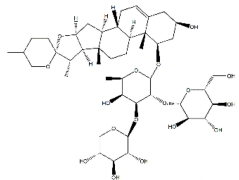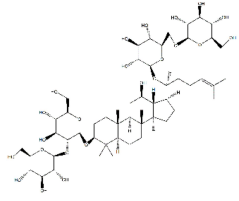
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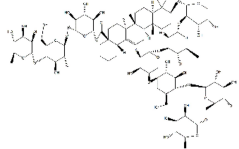| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Polysaccharides						
Fucoidan	*Sargassum*		MDA-MB-231 cells	Reducing the nuclear translocation and activity of HIF-1α, downregulation the expression levels of mesenchymal markers (N-cadherin and vimentin), but upregulating the expression levels of the epithelial markers (zonula occludens-1 and E-cadherin).	Mammary cancer.	[112]
Glycosides						
α-solanine	Potato, tomato, and eggplant.		Pancreatic cancer cell lines.	Retarding the growth of tumor cells by suppressing the expression of VEGF, E-cadherin and down-regulating ERK1/2/HIF-1α and STAT3 signaling pathways.	Pancreatic cancer.	[142]
Bufalin	Venenum Bufonis		The human HCC cell line SMMC7721	Suppressing HIF-1α expression through the inhibition of the PI3K/AKT/mTOR pathway, upregulation of E-cadherin, and downregulation of N-cadherin, vimentin, Snail.	Hepatocellular carcinoma.	[143]
			Six-week-old BALBc nu/nu mice inoculated with SMMC7721-GFP cells.	Significantly reducing liver/lung metastases, inhibiting EMT by up-regulating E-cadherin and down-regulating N-cadherin, vimentin, Snail.	Hepatocellular carcinoma.	[143]
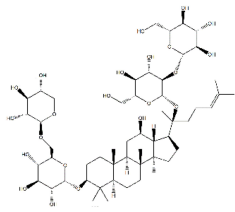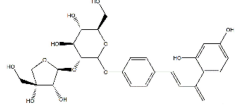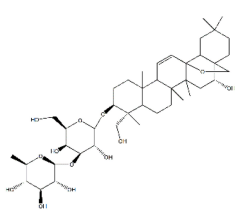
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Table 1 (Continued).

Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Clematichinenoside AR	*Clematis manshurica Rupr.; Clematis chinensis Osbeck; Clematis hexapetala Pall.*		NIH-3T3 cells.	Decreasing the expression of HIF-1α;	Arthritis.	[144]
			Female Wistar rats with collagen-induced arthritis (weighed 130–140 g)	Inhibiting hypoxic TGF-β1 induction and suppressing succinate-associated NLRP3 inflammasome activation by inhibiting SDH activity.	Arthritis.	[144]
Digoxin	*Digitalis*		C57BL/6J male mice placed on a high fat diet.	Digoxin directly bound to PKM2 and inhibited PKM2 targeting HIF-1α transactivation without affecting PKM2 enzyme activation, attenuated HIF-1α sustained NLRP3 inflammasome activation in macrophages.	Non-alcoholic Stsatohepatitis	[145]
DT-13 (13 of dwarf lilyturf tuber)	*Ophiopogon japonicus* (Linn. f.) Ker-Gawl.;		HUVECs	Suppressing tube formation and migration under both normoxia and hypoxia by down-regulating the expression of HIF-1α, p-ERK 1/2, p-Akt, VEGF and p-VEGFR2.	Cancers	[146]
Ginsenoside Rb1	*Panax ginseng* C. A. Mey; *Panax quiquefolium* L; *Panax notoginseng* (Burk.) F.H. Chen		ICR male mice (6–8 weeks), SD (200–250 g) rats and 1- or 2-days old neonatal rats.	Preventing hypoxic succinate accumulation in cardiomyocytes and improved PDH activity by blocking succinate-associated HIF-1α activation and GPR91 signaling.	Ischemia/Reperfusion (I/R) injury.	[147]
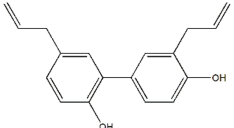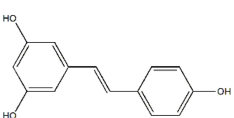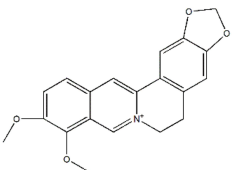
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Table 1 (Continued).

Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Ginsenoside Rb3	*Panax ginseng* C. A. Mey; *Panax quiquefolium* L; *Panax notoginseng* (Burk.) F.H. Chen		SKOV3 and 3AO cells.	Blocking EMT by promoting the ubiquitin proteasome-mediated degradation of HIF-1α, inhibiting the expression of NF-κB.	Ovarian cancer.	[148]
			Six-week old BALB/c female nude mouse inoculated with ovarian cancer.	Inhibiting tumor growth and also blocking EMT by promoting the ubiquitin proteasome-mediated degradation of HIF-1α.	Ovarian cancer.	[149]
Isoliquiritin apioside	Glycyrrhiza uralensis Fisch.		HT1080 cells	Inhibiting MMP-9, placental growth factor and VEGF by weakening the HIF-1α pathway, suppressing cell metastasis by inhibiting the activation of NF- κB.	Cancers.	[113]
Saikosaponin-d	*Bupleurum chinense* DC.; *Bupleurum scorzonerifolium* Willd.		SMMC-7721 cells	Inhibiting the proliferation and induces the apoptosis, inhibiting the expression of COX-2 via p-STAT3/HIF-1α pathway.	Hepatocellular carcinoma	[150]
Triterpenoid Saponins	*Camellia sinensis*		OVCAR-3 and A2780/CP70 cells.	Decreasing VEGF protein levels in a HIF-1α -dependent pathway.	Ovarian cancer	[151,152]
Polypeptides						
Melittin	Bee venom		SMMC-7721, Huh7, and Hep G2 cells, male Balb/c nude mice injected with SMMC-7721 cells (6–8 weeks old and weighed 20 ±2 g)	Decreasing the protein and mRNA levels of HIF-1α, p-Akt, VEGF and MMP-2/9, restraining EMT and vasculogenic mimicry formation in liver cance.	Liver cancer.	[114]
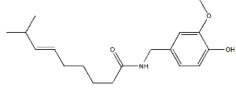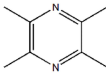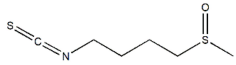
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Table 1 (Continued).

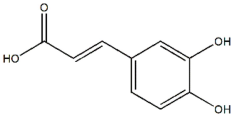| Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Polyphenols						
Caffeic Acid	*Solidago decurrens* Lour.		Cervical tumor cell lines C-4I	Alleviating glutamine anaplerosis by downregulation of Glutaminase (GLS) and Malic Enzyme 1 (ME1), altering TCA cycle supplementation with pyruvate via PDH, increasing ROS formation and enhancing cell death, inhibiting expression of HIF-1α.	Cervical cancer.	[153]
Honokiol	*Magnolia officinalis* Rehd. et Wils.		H460, A549, H358, H2122, BEAS-2B, NIH3T3, CCD19-Lu cells	Inducing G1 arrest and apoptosis, up-regulating Sirt3 and weakening the expression of HIF-1α.	Non-small cell lung cancer	[154]
Resveratrol	*Polygonum cuspidatum* Sieb.et Zucc.; grapes		BxPC-3, HepG2 and SKOV-3 cells	Inducing apoptosis and decreasing the expression of the β_2-adrenergic receptor (ADRB-2) and HIF-1α.	Pancreatic cancer	[155]
Alkaloids						
Berberine	*Coptis chinensis* Franch.; *Phellodendron chinense* Schneid.		SC-M1 cells, HUVEC	Inhibiting the stimulatory potential of hypoxic SC-M1 cells on HUVEC migration by repressing the expression of HIF-1α and VEGF in SC-M1 cells and promoting HIF-1α degradation via a proteasomal proteolytic pathway and lysine acetylation.	Gastric adenocarcinoma	[156]
			HCT116 and KM12C	Impeding hyperactive glucose uptake and glycolysis by suppressing mTOR-mediated HIF-1α synthesis.	Cancers.	[157]

(*Continued*)

Table 1 (Continued).

Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Capsaicin	*Capsicum annuum* L.		LNCaP cells	Decreasing nuclear AR, prostate specific antigen and Bcl-XL levels, reducing HIF-1 α stabilization.	Prostate cancer	[158]
Ligustrazine	*Ligusticum chuanxiong* Hort.		Human HSC-LX2 cells, rat HSC-T6 cells.	Inhibiting angiogenic cytokine production, migration, adhesion and contraction, activating PPARγ, activation of PPARγ by ligustrazine leading to transrepression of HIF-1α via a SMRT-dependent mechanism.	Hepatic fibrosis and cirrhosis.	[159]
Sulforaphane	Broccoli, cauliflower, brussel sprouts, cabbage, kale, kohlrabi, and so on.		LNCaP cells;	Decreasing nuclear AR, prostate specific antigen and Bcl-XL levels, reducing HIF-1 α stabilization.	Prostate cancer	[160]
			RT112 and RT4 cells	Inhibiting cell proliferation, decreasing glycolytic metabolism by downregulating hypoxia-induced HIF-1α and blocking HIF-1α translocation to the nucleus.	Bladder cancer	[160]

of mouse peritonitis. It is not only controlled by HIF-1α but also depends on the integrity of the NF-κB signaling pathway.[106] In order to explore the molecular mechanism of emodin in the treatment of intestinal barrier dysfunction, Caco-2 cells (a human colonic cell line) were co-incubated with lipopolysaccharide (LPS) and treated with hypoxia/ reoxygenation to induce barrier dysfunction. In this experiment, the scholars were surprised to find that the paracellular permeability of Caco-2 cells was reduced after emodin treatment, and the levels of NF-κB and HIF-1α protein were significantly reduced, while the damage to cells caused by LPS and hypoxia/reoxygenation has also been alleviated. The above results indicate that emodin may protect the intestinal epithelial barrier dysfunction caused by inflammation and hypoxia by inhibiting HIF-1α and NF-κB signaling pathways.[96,107] Subsequent studies on pancreatic cancer cells have shown that in addition to emodin, rhein,

another anthraquinone compound in Dahuang, also regulates HIF-1α. In previous studies, we know that Akt and ERK1/2 signaling pathways can induce HIF-1α expression by increasing HIF-1α biosynthesis. In the study on pancreatic cancer, the researchers further clarified that rhein and emodin can reduce the content of HIF-1α regardless of whether it is under normoxia or hypoxia. What is more, this process is achieved by inhibiting Akt and ERK1/2 signaling pathways to reduce the biosynthesis of HIF-1α, rather than by affecting the gene transcription or protein stability of HIF-1α. Besides this, emodin and rhein also can inhibit the growth of cancer cells by inhibiting their proliferation rather than inducing cell death.[108] In addition to Dahuang, there are many natural medicines that contain quinones, and they also have inhibitory effects on HIF-1α. For example, Cassiae Semen (named "Juemingzi" in Chinese) is dry, mature seed of the leguminous plant

Cassia obtusifoiia L. or *Cassia tora* L. The quinones extracted from it, obtusifolin can treat choroidal neovascularization by affecting the content of HIF-1α. In previous studies, it has been clarified that hypoxia is an important cause of choroidal neovascularization, and VEGF plays an extremely important role in this disease. In an in vitro hypoxia model of ARPE-19 cells induced by cobalt chloride ($CoCl_2$), the mRNA and protein levels of HIF-1α, VEGF, and VEGFR2 in the cells decreased significantly after obtusifolin treatment, while their transcription and translation processes were inhibited. At the same time, obtusifolin also reduces cell viability under hypoxic conditions and arrests G1 phase cells to treat choroidal neovascularization from many aspects.[109]

Terpenoids and polysaccharides can be also beneficial for regulation of the content of HIF-1α. Celastrol, also known as tripterine, is a quinine methide triterpenoid compound extracted from the Chinese herb *Tripterygium wilfordii* HOOK F. It can decrease PPARβ, HIF-1α and elevate p53 in HepG2 cells. At the same time, celastrol inhibits hepatocellular carcinoma survival by inducing cells apoptosis.[110] Another diterpene compound, oridonin, derived from the TCM of Rabdosiae rubescentis Herba, has anti-metastatic effect in breast cancer treatment by inhibiting epithelial–mesenchymal transition (EMT) and the HIF-1α/VEGF signaling pathway. After treatment with oridonin, the expression of E-cadherin decreased, while the expression of N-cadherin, Vimentin, Snail, HIF-1 α, VEGF-A and VEGFR2 increased.-[111] Polysaccharides are a class of macromolecular substances composed of a large number of monosaccharides, some of which have significant inhibitory effects on HIF-1α. For example, fucoidan extracted from Brown seaweed is a kind of sulfated polysaccharide, which has a significant therapeutic effect on mammary cancer. It not only reduces the protein level of HIF-1α but also inhibited the nuclear translocation of HIF-1α. In addition, it inhibits epithelial–mesenchymal transformation by down-regulating N-cadherin and vimentin and up-regulating ZO-1 and E-cadherin.[112]

Apart from the above compounds, a variety of components that inhibit HIF-1α, including glycosides, peptides, polyphenol and so on. For instance, isoliquiritin apioside, a component isolated from Glycyrrhizae radix et Rhizoma, has been found to exert anti-cancer effects. Isoliquiritin apioside can inhibit matrix metalloproteinase-9 (MMP-9), placental growth factor and VEGF by weakening the HIF-1α pathway, thus playing an anti-angiogenic effect. In addition, it has no significant inhibitory effect on cell proliferation but can suppress cell metastasis by inhibiting

the activation of NF- κB.[113] Melittin is a kind of polypeptide, which is the main component of bee venom. It can decrease the protein and mRNA levels of HIF-1α, p-Akt, VEGF and MMP-2/9. Besides that, melittin also can restrain EMT and vasculogenic mimicry formation in liver cancer.[114] Other bioactive components found at present are shown in Table 1.

Compound Traditional Chinese Medicine Preparation

Compound traditional Chinese medicine (TCM) preparations have been used for thousands of years in Asian countries such as China, Korea, and Japan. With the development of modern medicine, researchers have found that many compound TCM preparations also have an inhibitory effect on the content of HIF-1α. Buyang Huanwu Decoction (BYHW) is a classic prescription for the treatment of stroke. It was first recorded in the literature of Correction on Errors in Medical Works in the Qing Dynasty in 1830. The formula mainly contains seven Chinese herbs, namely: (1) Astragali Radix; (2) Angelicae sinensis Radix; (3) Paeoniaeradix Rubra; (4) Pheretima; (5) Rhizoma Chuanxiong; (6) Carthami Flos; (7) Persicae Semen, while the four components with the highest content in BYHWD are calycosin-7-O-β-D-glucoside, ononin, calycosin and formononetin.[115,116] In modern clinical practice, BYHW is widely used in the treatment and prevention of ischemic cardiovascular vascular diseases. Cerebral ischemia and reperfusion may lead to serious consequences such as damage to the blood-brain barrier and brain edema, thereby causing additional loss of brain tissue. Therefore, reducing the permeability of the blood-brain barrier and the severity of cerebral edema is important for the development of cerebral ischemia treatment. In hypoxia or cerebral ischemia, the content of HIF-1α will increase rapidly, promoting the expression of its downstream target genes such as erythropoietin and VEGF, which will increase the vascular permeability and the area of cerebral infarction. In previous studies, it has been known that BYHWD can down-regulate apoptosis-related genes, inhibit inflammation and angiogenesis, and can also up-regulate neurodevelopment-related genes to protect mice from ischemic stroke. But at that time, the specific mechanism was unclear.[115] On this basis, after further research, scholars found that after BYHWD was used to treat mice, the HIF-1α/VEGF pathway was inhibited and protein expression decreased. At the same time, the transcription and translation of β-EnaC in the body increase, the blood–brain barrier is effectively protected,

the area of brain edema is reduced, and the symptoms of cerebral infarction are alleviated. In summary, we can think that BYHWD can maintain the integrity of the blood-brain barrier and treat ischemic stroke by inhibiting the HIF-1α/VEGF pathway.[116]

In addition, there are other compound TCM preparations, such as Yi Ai Fang, Shaofu Zhuyu Decoction, and Shengui Sansheng San, which can exert corresponding therapeutic effects by inhibiting HIF-1α. See Table 2 for details.

Promotion of HIF-1α

Bioactive Components

Currently, many researches have focused on the inhibitory effect of medicine on HIF-1α, while there have been far fewer studies on drugs promoting HIF-1α. Rhodiolae Crenulatae Radix et Rhizoma (*Rhodiola*), the root and rhizome of *Rhodiola crenulata* (Hook. f. and Thoms.) H. Ohba has been used as a medicine for thousands of years. *Rhodiola* is mostly used to enhance the body resistance against hypoxia in mountain sickness, but its mechanism has only been gradually revealed in the past decade. First, it was found that the water extract deriving from *Rhodiola* can induce the expression of erythropoietin (EPO) in liver and kidney cells, increasing the level of mRNA and protein. As we all know, EPO is a key factor in regulating body balance under hypoxic environment, and it is also an erythrocyte-specific hematopoietic hormone that can increase red blood cell production. Application of water extract deriving from *Rhodiola* promotes the expression of EPO, so that the body can better adapt to the hypoxic environment.[89] Subsequently, the research team discovered that salidroside, a glycoside found in *Rhodiola*, is the main active substance of *Rhodiola* against hypoxia. Meanwhile, after using salidroside to co-incubate with human embryonic kidney fibroblasts (HEK293T) and human hepatocellular carcinoma HepG2 cells, the HIF-1α mRNA content did not change significantly, but the protein degradation became less, which eventually led to protein accumulation. The high expression of HIF-1α stimulated the expression of EPO mRNA from its transcription regulatory element HRE, located on EPO gene, which in turn increases the level of EPO mRNA and protein, so that cells can better adapt to the hypoxic environment.[117] Interestingly, in the study of osteoblasts, it was discovered that salidroside can accelerate the healing of fractures from both cell-autonomous and non-autonomous aspects by regulating the MAPK/ERK and PI3K/Akt signaling pathways. First, salidroside can

improve cell viability by changing the cycle of osteoblasts, and induce the expression of RunX2 and osteoblasts to promote cell differentiation and mineralization. In in vitro experiments, salidroside can increase the transcriptional activity of HIF-1α, promote nuclear translocation, thereby increase the expression of VEGF, induce angiogenesis, and accelerate fracture healing.[118] Thus, it can be seen that although salidroside can increase the content of HIF-1α in different models, its effects are not the same. The rest are shown in Table 3.

The same active ingredient can not only increase the content of HIF-1α in different ways but also produce two distinct effects on the content of HIF-1α in different models. As mentioned in Table 3, tanshinone IIA can inhibit the growth and proliferation of HepG2 cells under hypoxic conditions and induce apoptosis. At the same time, the expression of HIF-1α and VEGF is reduced, while p53 is up-regulated, thereby producing a therapeutic effect on hepatocellular carcinoma.[119] However, when studying myocardial infarction model rats, it was found that tanshinone IIA can promote angiogenesis by increasing the mRNA expression of HIF-1α and VEGF, improve heart function, and reduce the infarct size.[120] Other bioactive ingredients found so far are shown in Table 3.

Compound Traditional Chinese Medicine Preparation

There are also some compound traditional Chinese medicine preparations that can treat related diseases by increasing the level of HIF-1α. Houshihesan (HSHS) is a classic prescription of traditional Chinese medicine for the treatment of stroke, which has been used safely and effectively in clinical treatment for nearly 2000 years. HSHS consists of the following 13 traditional Chinese herbs: Chrysanthemi Flos, Saposhnikoviae Radix, Cinnamomi Ramulus, Chuanxiong Rhizoma, Asari Radix et Rhizoma, Platycodonis Radix, Atractylodis macrocephalae Rhizoma, Poria, Zingiberis Rhizoma, Angelicae sinensis Radix, Ginseng Radix et Rhizoma, Scutellariae Radix and Ostreae Concha. In the experiment, a permanent middle cerebral artery occlusion model was established in rats. After intragastric administration of HSHS with different doses, the symptoms of angioedema in rats were obviously alleviated, and the damage of blood vessels and neurons in the ischemic area was reduced. At the same time, the results of real-time fluorescent quantitative PCR and Western blot showed that HSHS can significantly promote the expression of HIF-1α, and increase the expression of VEGF and VEGFR2 in rats, while the expression of stromal cell-derived factor-1 (SDF-1) decline.

Table 2 Traditional Chinese Medicine Prescription That Can Inhibit HIF-1α

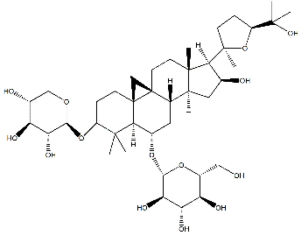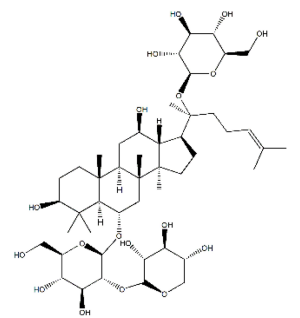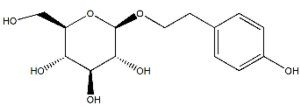| TCM Formulas	Composition	Experimental Models	Mechanism	Diseases	Refs.
Buyang Huanwu Decoction	Astragali Radix, Angelicae sinensis Radix, Paeoniaeradix Rubra, Pheretima, Rhizoma Chuanxiong, Carthami Flos, Persicae Semen	Male SD rats (weighted 190–210g) after occlusion of the right middle cerebral artery	Inhibiting the activation of the HIF-1α/VEGF pathway and increasing the transcription and translation of β-ENaC.	Ischemia Stroke.	[115,116]
Jianpi Qingchang Decoction	Astragali Radix, Codonopsis Radix, Portulacae Herba, Sanguisorbae Radix, Notoginseng Radix et Rhizoma, Bletillae Rhizoma, Aucklandiae Radix, Coptidis Rhizoma, Glycyrrhizae Radix et Rhizoma	Male C57BL/6 mice (8 weeks old) stimulated by administration of 3.5% dextran sulfate sodium.	Improving the mucosal inflammatory response and intestinal epithelial barrier function by inhibiting the NF-κB/HIF-1α signalling pathway.	Ulcerative colitis	[161]
Longshengzhi Capsules	Astragali Radix, Carthami Flos, Angelicae Sinensis Radix, Chuanxiong Rhizoma, Persicae Semen, Paeoniaeradix Rubra, Aucklandiae Radix, Acori Tatarinowii Rhizoma, Talxilli Herba, Siberian Ginseng.	Adult male SD rats (weight 250–280g)	Decreasing brain edema, ROS and inflammatory factor levels, increasing activities of SOD, neurosynaptic remodeling, downregulating MMP-2/9, VEGF and NF-κB, upregulating Map-2 and GAP-43 via p38 MAPK and HIF-1α signaling pathways	Ischemic stroke outcomes and reperfusion injury	[162]
Qingshen Granules	Hedyotidis diffusae Herba, Coptidis Rhizoma, Artemisiae scopariae Herba, Rhei Radix et Rhizoma, Coicis Semen, Atractylodis macrocephalae Rhizoma, Lablab Album Semen, Poria, Salviae Miltiorrhizae Radix et Rhizoma, Leonuri Herba, Alismatis Rhizoma, Polyporus, Plantaginis Herba, Amomi Rotundus Fructus	Patients diagnosed with chronic kidney disease and damp-heat syndrome of TCM (aged between 18 and 70 years old)	Reducing the levels of α-SMA and E-cadherin in peripheral blood and regulating the levels of HIF-1α, Wnt1, and β-catenin in serum	Chronic renal failure	[95]
Shaofu Zhuyu Decoction	Foeniculi Fructus, Zingiberis Rhizoma, Corydalis Rhizoma, Myrrha, Rhizoma Chuanxiong, Angelicae Sinensis Radix, RadixPaeoniae Rubra, Cortex Cinnamomi, Typhae Pollen, and Trogopteri Feces	Adult female SD rats (weighed 180–220g) with endometriosis induced by autologous transplantation	Decreasing cell proliferation, microvessel density and the expression of HIF-1α, increasing cell apoptosis	Endometriotic lesions	[94]
Shengui Sansheng San	Ginseng Radix et Rhizoma, Angelicae sinensis Radix, Cortex Cinnamomi	BMECs cells, SD rats after occlusion of the right middle cerebral artery	Improving neurological functional scores, survival rate and cerebral infarct volume, enhancing vWF+ vascular density and perimeter, SDF-1α/CXCR4 axis, VEGF expression, as well as activating AKT/mTOR/HIF-1α and ERK1/2 and inhibiting Notch1 pathways in penumbra; increasing BMEC migration, capillary formation and VEGF expression via up-regulations of AKT/mTOR and ERK1/2 pathways in vitro	Ischemic stroke	[163]

(*Continued*)

Table 2 (Continued).

TCM Formulas	Composition	Experimental Models	Mechanism	Diseases	Refs.
Tongxinluo	Ginseng Radix et Rhizoma, Hirudo, Scorpio, Paeoniaeradix Rubra, Cicadaeperiostracum, Eupolyphaga Steleophaga, Scolopendra, Santali Albi Lignum, Dalbergiae Odoriferae Lignum, Olibanum, Ziziphispinosae Semen, Borneolum Syntheticum.	Human cardiac microvascular endothelial cel	Decreasing COX 2, iNOS, HIF-2α, HIF-1α, VEGF, PGE 2 and NT contents, attenuating the inflammatory and oxidative injury	Endothelial dysfunction	[164]
Weipixiao	Astragali Radix, Pseudostellariae Radix, Atractylodis Macrocephalae Rhizoma, Curcumae Rhizoma, Salviae miltiorrhizae Radix et Rhizoma, Hedyotis Diffusa Willd	Male SD rats with MNNG-induced gastric precancerous lesions	Suppressing HIF-1α mRNA and protein expression, inhibiting VEGF protein expression and the ERK1/Cylin D1 aberrant activation	Gastric precancerous lesions.	[165]
Weiqi Decoction	Angelicae Sinensis Radix, Astragali Radix, Codonopsis Radix, Curcumae Longae Rhizoma, Aurantii Fructus, Akebiae Caulis, Taraxaci Herba	Male Wistar rats with 160–180 g	Decreasing the protein and gene expression of COX-2, HIF-1α, VEGFR1, and VEGFR2, increasing cell apoptosis	Chronic atrophic gastritis.	[166]
Xin-Sheng-Hua Granule	Angelicae sinensis Radix, Leonuri Herba, Chuanxiong Rhizoma, Persicae Semen, Zingiberis Rhizoma Praeparatun, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Carthami Flos	The blood deficiency female rats (weighed 220–250 g) induced by bleeding from orbit	Regulating coenzyme A biosynthesis, sphingolipids metabolism and HIF-1α pathways, which was reflected by the increased levels of EPOR, F2, COASY, as well as the reduced protein expression of HIF-1α, SPHK1, and S1PR1	Anemia	[167,168]
Yi Ai Fang	Astragali Radix, Atractylodis macrocephalae Rhizoma, Actinidia arguta, Curcumae Rhizoma, Benincasa hispida	HCT-116, Babl/c nude male mice inoculated with HCT-116 cells (weighed 18±2 g)	Enhancing expression of E-cd and Claudin-4, and decreasing expression of HIF-1α, vimentin in vitro and vivo	Colorectal cancer	[169]
Yifei Huoxue Granule	Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Angelicae sinensis Radix, Carthami Flos, Prunus persica, Cyathulae Radix, Rehmannia Radix, Chuanxiong Rhizoma, Paeonia lactiflora pall, Citri Reticulatae Pericarpium, Bupleuri Radix, Citrus aurantium L., Platycodonis Radix, Platycodon	PASMCs	Inhibiting hypoxia-induced proliferation of rat PASMCs, decreasing the expression of HIF-1α and attenuating the hypoxia-induced increase in intracellular concentration of ROS and Ca^{2+}	Hypoxic pulmonary hypertension	[170]

Among them, SDF-1 can specifically bind to the CXC chemokine receptor 4 (CXCR4), guide the migration of endothelial cells, and extend the ischemic blood vessels to areas with sufficient blood supply. In addition, the HSHS drug serum was used in vitro test, and the results showed that HSHS significantly promoted the proliferation and migration of HUVECs under hypoxic conditions. The expression trend of related factors was consistent with the in vivo results. HIF-1α, VEGF, SDF-1 and CXCR4 and other related factors have increased expression.[121] Other compound traditional Chinese medicine preparations are shown in Table 4.

Conclusion and Perspectives
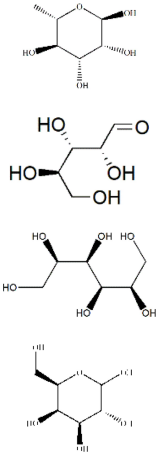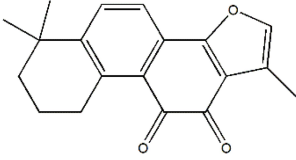
Taken together, all the collected evidences suggested that natural medicines and TCM formulas would be beneficial for treating various diseases (in particular for the tumors) through regulating HIF-1α. However, most of the studies only focus on the inhibitory effects of natural medicines and TCM formulas on HIF-1α, and just few studies go deep into the way through which they affect a certain step in the synthesis of HIF-1α. Besides that, there are few studies on the promotion effect of HIF-1α, and most of the experimental results are only from animal experiments

Table 3 Bioactive Components of Natural Medicine That Can Promote HIF-1α

Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Glycosides						
Astragaloside IV	*Astragalus propinquus* Schischkin		HUVECs	Promoting cell proliferation and stimulated HIF-1α accumulation by PI3K/Akt pathway, not affecting the degradation of HIF-1α protein or the level of HIF-1α mRNA, inducing the nuclear translocation of HIF-1α.	Myocardial ischemia	[171]
Notoginsenoside R1	*Panax notoginseng* (Burk.) F.H. Chen		Male SD rats (200 ± 20 g) with cisplatin	Reducing the levels of ROS, MDA and NO, as well as the opening of MPTP, increasing the levels of HIF-1α mRNA, SOD, CAT and GSH, as well as ATP and MMP in renal tissues.	Mitochondrial damage induced by cisplatin	[172]
Salidroside	*Rhodiola rosea* L.		Neonatal rat cardiomyocyte	Up-regulating the HIF-1α and VEGF protein expression, inducing HIF-1α translocation;	Heart failure	[173]
			HEK293T, HepG2 cells	Inducing the expression of EPO mRNA from its transcription regulatory HRE, stimulating the accumulation of HIF-1α by inhibiting HIF-1α degradation	Mountain sickness	[89,117]
			ROB, MG-63 cells	Stimulating osteoblast differentiation and mineralization by inducing the expression of Runx2 and Osterix, up-regulating HIF-1α expression at the mRNA and protein levels via MAPK/ERK and PI3K/Akt signaling.	Fracture	[118]

(*Continued*)

Table 3 (Continued).

Compounds	Original Plants	Chemical Structure	Models	Mechanism	Disease	Refs.
Polysaccharides						
Rhamnose, xylose, mannose, galactose, glucose	Enteromorpha Prolifera		HCMVEC;	Protecting HCMVEC from OGD-induced viability loss, proliferation inhibition, apoptosis, inflammatory cytokine expression, and autophagy, enhancing the expression of HIF-1α in HCMVEC via the MEK/ERK pathway, attenuating OGD-induced NF-κB pathway activation and promoted the mTOR pathway in HCMVEC;	Acute myocardial infarction	[174]
			Wistar rats pre-treated by PEP	Reducing the infarct size and enhancing the LVEDD, LVEF and LVFS of rats via up-regulation of HIF-1α.	Acute myocardial infarction	[174]
Quinones						
Tanshinone IIA	Salvia miltiorrhiza Bge.		Male SD rats weighing 200-	Improving heart function, reducing infarct size, and increasing survival rate, up-regulating the expression of HIF-1α and VEGF.	Myocardial ischemia	[120]
			220 g (aged 10 weeks) with myocardial infarction	Improving heart function, reducing infarct size, and increasing survival rate, up-regulating the expression of HIF-1α and VEGF.	Myocardial ischemia	[120]

or in vitro cell experiments, which cannot effectively explain the problem. Therefore, it is recommended that in future research, more attention can be devoted to the promotion of HIF-1α by natural products or TCM formulas, and a combination of in vivo and in vitro methods should be adopted to further study its effect. Recent studies have shown that many natural products can not only affect HIF-1α content by themselves but also reduce the side effects of drugs when used in combination with other marketed drugs. We believe that discovering the effect of natural products on HIF-1α from the perspective of

combined medicine is also the future research direction. Although the limited clinical trials are not perfect in quality, they still have certain reference value. In the future, we need more scientific and representative clinical trials.

A variety of active ingredients can be extracted from natural medicines, but in the current research, we have only found that some monomer ingredients can affect the content of HIF-1α, and these ingredients are more concentrated in flavonoids, terpenes and glycosides. So there are more active monomers to be discovered. We hope that this review can provide a scientific basis for existing natural

Table 4 Compound Traditional Chinese Medicine Preparation That Can Promote HIF-1α

TCM Formulas	Composition	Models	Mechanism	Disease	Refs
Houshiheisan	*Chrysanthemi Flos, Saposhnikoviae Radix, Cinnamomi Ramulus, Chuanxiong Rhizoma, Asari Radix et Rhizoma, Platycodonis Radix, Atractylodis macrocephalae Rhizoma, Poria, Zingiberis Rhizoma, Angelicae sinensis Radix, Ginseng Radix et Rhizoma, Scutellariae Radix and Ostreae Concha.*	Im-HUVECs	Promoting cell proliferation and migration, up-regulating the expression of HIF-1α, VEGFA, Ang-1, Ang-2, and CXCR4, down-regulating Ang-2.	Ischemic cerebral stroke.	[121]
		Three-month-old male SD rats with permanent middle cerebral artery occlusion.	Alleviating blood vessel edema, reducing the damage to blood vessels and neurons in the ischemic areas, up-regulating pro-angiogenic factors includingCD31, VEGF, VEGFA, VEGFR2, Ang-1, while down-regulating Ang-2, SDF-1, and CXCR4 expression in infarct rat cortex.	Ischemic cerebral stroke.	[121]
Qi-Shen-Yi-Qi Dripping Pills	*Astragali Radix, Salviae miltiorrhizae Radix et Rhizoma, Notoginseng Radix et Rhizoma, Dalbergiae Odoriferae Lignum.*	Male SD rats (220g-280g) with myocardial infarction.	Up-regulating the gene and protein expression of HIF-1, VEGF, MAPK, PI3K, and AKT, downregulating mir-223-3p expression, regulating angiogenesis of ischemic CMECs.	Ischemic heart disease.	[175]
Wenshen Yangxue decoction	*Cistanches Herba, Cervi Cornu, Epimedii Folium, Cuscutae Semen, Lycii Fructus, Rubi Fructus, Lycopi Herba, Leonuri Herba, Achyranthis bidentatae Radix, Spatholobi Caulis, Carthami Flos, Salviae miltiorrhizae Radix et rhizome, Angelicae sinensis Radix, Typhae Pollen, Bupleuri Radix, Cyperi Rhizoma, Aucklandiae Radix, Paeoniae Radix Rubra, Chuanxiong Rhizoma, Rehmanniae Radix Praeparata, Corni Fructus, Notopterygii Rhizoma et Radix, Asari Radix et Rhizoma.*	Proestrus female and male rats were fed with saline and hydroxyurea solution.	Increasing the blastocyst number, promoting endometrial angiogenesis through PI3K, HIF-1α signalling and VEGF expression regulation.	Impaired endometrial receptivity.	[13]

medicines and TCM formulas to affect HIF-1α content, further clarify the market positioning, and provide guidance for the development of new products in the future.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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