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•Review•

HIF-1: structure, biology and natural modulators

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[ABSTRACT] Hypoxia-inducible factor 1 (HIF-1), as a main transcriptional regulator of metabolic adaptation to changes in the oxygen environment, participates in many physiological and pathological processes in the body, and is closely related to the pathogenesis of many diseases. This review outlines the mechanisms of HIF-1 activation, its signaling pathways, natural inhibitors, and its roles in diseases. This article can provide new insights in the diagnosis and treatment of human diseases, and recent progress on the development of HIF-1 inhibitors.

[KEY WORDS] Hypoxia; Natural product; Human disease; Inhibitor
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Introduction

Hypoxia is ubiquitous in the cells and tissues of organisms, which can lead to metabolic disorders and even organ failure [1]. Hypoxia-inducible factor 1 (HIF-1) and its signaling pathways play an important role in metabolic adaptation to hypoxia stress [2-4]. HIF-1 is a specific transcription factor which is active under hypoxic conditions. Meanwhile, HIF-1 participates in many important physiological processes such as cardiovascular generation, cartilage development, neural embryo formation, and tumor development, and is closely related to various pathological processes in humans [5-7]. Furthermore, HIF-1 is directly associated with tumor radio- and chemo-therapy resistance and prognosis [8]. With respect to the important role of HIF-1, increasing attention has been drawn on the development of HIF-1 modulators [9]. So far, many HIF-1 modulators have been reported, and some small anti-tumor molecules have been assessed in clinical trials. Interestingly, the world's first oral HIF-1 inhibitor was approved for the treatment of renal anemia. This review summarizes the classical signaling pathways of HIF-1, its regulatory mechanisms and representative inhibitors derived from natural products.

HIF-1 Classical Signaling Pathways

HIF-1 was originally identified in 1991 by Semenza and co-workers [10]. During that study, one DNA sequence (5′-RCGTG-3′) was discovered in the 3′-flanking region of the erythropoietin (EPO) gene [4]. The DNA sequence played a key role in the transcription activity of genes under hypoxic conditions, and was then known as hypoxia response elements (HREs) [11]. After binding to HRE, the related genes were activated at transcriptional level by a specific protein which was produced under hypoxia conditions and later known as HIF-1 [12].

HIF-1 is a heterodimeric transcription factor consisting of a constitutive β-subunit and an oxygen-sensitive α-subunit [13]. HIF-1α is one of three HIF-α isoforms (in addtion to

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HIF-2α and HIF-3α) in humans, whose expression is protected under hypoxia conditions [14]. HIF-2 and HIF-1 are regulated in a similar manner (hydroxylation under normoxic conditions), but their activities are not exactly the same [15]. In contrast, HIF-3α is a tissue-specific protein that exists in various spliced variants [16]. Furthermore, HIF-1β is an aryl carbon receptor nuclear translocator (ARNT), which binds to the aryl hydrocarbon receptor, followed by promoting its translocation to the nucleus [17].

Both HIF-1α and HIF-1β belong to the bHLH-PAS protein family of transcription factors, due to their structures with two nuclear proteins (Per and Sim, PAS) and basic-helix-loop-helix (bHLH) motifs [18]. The bHLH-PAS motifs mediate the formation of the HIF-1α/β complex, while the two transcriptional activation domains (C-TAD and N-TAD) of HIF-1α recruit co-activator proteins to form active transcriptional complexes and bind to HRE (Fig. 1) [19]. C-TAD regulates the transcription of HIF-1α under hypoxia conditions [20]. In contrast, N-TAD is a regulator for the stabilization of HIF-1α [21].

In general, HIF-1α has a short half-life (5 min) due to its rapid degradation by the von Hippel-Lindau tumor suppressor protein (VHL), which mediates degradation *via* the ubiquitin-proteasome system under normoxic conditions (Fig. 2). VHL, a recognized component of an E3 ubiquitin-protein ligase, can directly bind to hydroxylated HIF-1α [22, 23]. Then, the VHL/HIF-1α complex can be easily recognized by the proteasome [24]. However, HIF-1α hydroxylation only occurs in a

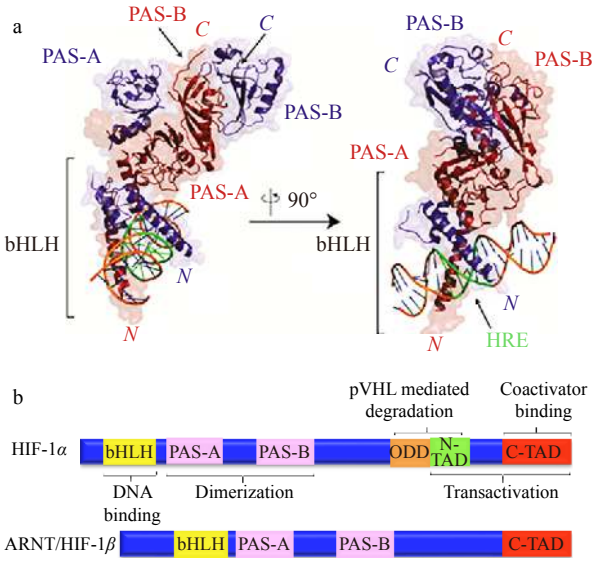

Fig. 1 Schematic structure of HIF-1. a) X-ray crystal structure of HIF-1 (PDB ID: 4ZPR). Domains in HIF-1 subunits are indicated, and HRE (hypoxia response element) is highlighted in green. b) Functional domains of HIF-1. bHLH: basic helix-loop-helix domain; PAS: Per/ARNT/Sim domain; ODD: oxygen dependent degradation domain; N-TAD: *N*-terminal transactivation domain; C-TAD: *C*-terminal transactivation domain. Panel a is adapted with permission from REF. 13. © (2015) Elsevier

condition with sufficient oxygen. Under hypoxic conditions, hydroxyl reductase is inactivated, so HIF-1α cannot be hy-

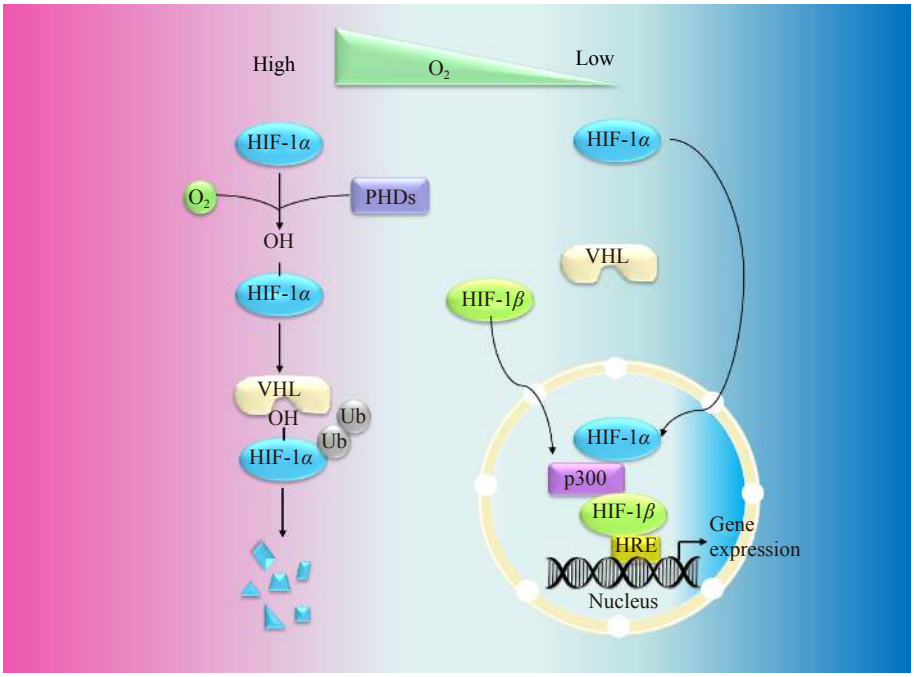

Fig. 2 von Hippel-Lindau tumor suppressor protein (VHL)-dependent HIF-1α signaling pathways. Under normoxia conditions, HIF-1α protein is recognized by prolyl hydroxylase protein (PHD), before combination with von Hippel-Lindau protein (VHL) and ubiquitination (Ub). It is subsequently degraded by the proteasome. Under hypoxia conditions, PHD is inactivated. HIF-1α and HIF-1β translocate to the nucleus, thus forming a complex with p300 in the nucleus, binding to hypoxic response element (HRE) and activating gene transcription

droxylated, which prevents degradation by the proteasome [25]. The surviving HIF-1α dimerizes with HIF-1β to form a heterodimer that translocates into the nucleus [26]. The heterodimer binds to p300 and forms a transcriptional activation complex, which can recognize the HRE-DNA site and activate the transcription of HIF-1 target gene, such as vascular endothelial growth factor (VEGF), glucose transporter 1 (GLUT1) and EPO (Fig. 2) [27-29].

Regulation of the HIF-1α Pathway

The transcriptional activity and stability of HIF-1α are regulated by several pathways through post-translational modifications including phosphorylation, hydroxylation, acetylation and ubiquitination [23, 30-32].

Oxygen-dependent stabilization of HIF-1α

The expression of HIF-1α is regulated by proteasomal degradation and ubiquitination pathway, which involves hydroxylases (namely factor inhibiting HIF, FIH) and VHL. The hydroxylation of HIF-1α by 2-OG-dependent dioxygenase enzymes prolyl-4-hydroxylases (PHDs) occurs under normoxia conditions [33]. The expression of arrest-defective-1 (ARD-1), an enzyme responsible for the acetylation of HIF-1α, decrease under hypoxia conditions [16]. Hence, reduced hydroxylation or acetylation of HIF-1α under hypoxia can lead to an accumulation of HIF-1α (Fig. 3).

Another oxygen-dependent regulation of HIF-1α activity under normoxia conditions is performed through the control of HIF-1α and p300 interaction, which is an important mechanism for the regulation of post-translational modification mediated by HIF-1α transactivation (Fig. 3) [34]. The gene transcription of HIF-1α targeting genes is initiated by the binding between the co-activators CBP/p300 and C-TAD of HIF-1α [35]. Under normoxia conditions, the hydroxylation of HIF-1α by asparaginyl hydroxylase interrupts the interaction between p300 and HIF-1α in an oxygen-dependent manner, thereby leading to the inactivation of HIF-1α [36, 37].

Oxygen-independent stabilization of HIF-1α

There are several pathways that are associated with tumorigenesis, without the involvement of hydroxylases, and believed to contribute to the accumulation of HIF-1α. For example, extracellular-signal-regulated kinase (ERK) controls both the synthesis and transcriptional activation of HIF-1α [38]. ERK can also phosphorylate p300, which induces the formation of the HIF-1/p300 complex and enhances their transcriptional activity [39]. Previous reports showed that knockdown of the tumor suppressor gene p53 increased HIF-1α levels in human colon cancer [40]. The possible explanation is that p53 can recognize and bind to HIF-1α to stimulate ubiquitination and degradation of HIF-1α via the mouse double minute 2 homolog (Mdm2) [21]. Loss or mutation in p53 alleviates Mdm2-mediated HIF-1 degradation in tumors [41]. Hsp90 inhibitors reduces the levels of HIF-1α by ignoring the availability of oxygen [42]. In general, Hsp90 directly binds to HIF-1α, resulting in conformational changes in its structure, and changes the transactivation of the initial binding to HIF-1β [43]. In addition, Hsp90 stabilizes HIF-1α against degradation (Fig. 3) [44].

HIF-1 and Diseases

HIF-1 mediates the body's responses to hypoxic microenvironment, induces the angiogenesis, migration and proliferation of fibroblasts and keratinocytes, anaerobic metabolic transformation, and systemically increases the number of red blood cells [45]. Therefore, stabilization of HIF-1 is of great significance for the treatment of anemia and wound healing [46]. It has been reported that HIF-1 stabilizer FG-2216 can increase the level of EPO in hemodialysis patients [47]. Currently, several compounds, including FG-4592 (roxadustat) and JTZ-951, are being assessed in clinical trials

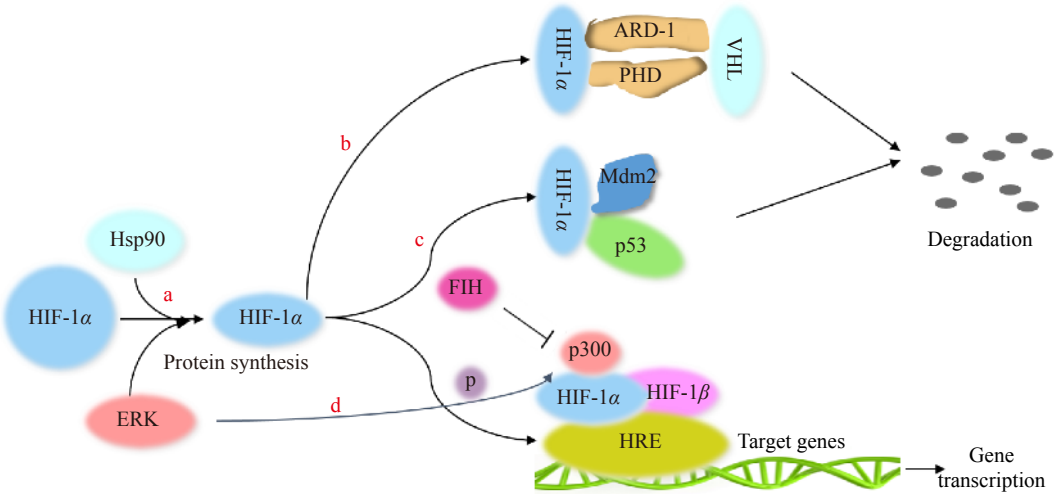

Fig. 3 Regulation of the HIF-1α pathway at different levels. (a) Heat shock protein 90 (Hsp90): Rat sarcoma/rapidly accelerated MAPK/ERK kinase. (b) Protein von Hippel-Lindau (pVHL) pathways. (c) Mdm2-p53 mediated ubiquitination and proteasomal degradation pathway. (d) Factor-inhibiting HIF (FIH-1) pathway. These pathways regulate HIF-1 activity through regulating HIF-1 synthesis, stability (a, b, c) and transactivation (c, d)

for the treatment of renal anemia [47].

HIF-1α and VEGF proteins are found to be co-localized in endothelial cells with ethanol-induced acute gastric mucosal injury [48]. The level of VEGF protein significantly increases in the necrotic gastric mucosa. Furthermore, the expression of HIF-1α and VEGF proteins significantly increases in esophageal tissue after ulcer induction, indicating that HIF-1α is involved in the activation of VEGF gene in regenerating microvessels during esophageal ulcer healing [49].

The activation of HIF-1α can also induce collateral angiogenesis and improve myocardial blood supply in ischemic heart disease [50]. Therefore, up-regulation of HIF-1α can significantly increase red cell mass and reduce the damage of ischemic tissues. Other studies have also shown that HIF-1α can be a biomarker for predicting heart damage in patients with chronic hypoxia [29].

HIF-1 is abnormally expressed in the kidneys of diabetic kidney disease (DKD) patients, and its expression is associated with tubular injury [51]. In addition, the HIF-1 system is often activated before tubulointerstitial injury, while HIF-1α is highly expressed in the kidneys of diabetic mice. Chiu *et al*. proposed the hyperglycemia-HIF pathways; hyperglycemia can activate HIF *via* several ways under normoxia or hypoxia conditions, such as PKC activation, the formation of advanced glycation end products , mitochondrial ROS, proinflammatory cytokines, and rage signaling, etc. [52]. This may reduce HIF-1 degradation and activate nuclear factors by damaging the proteasome HIF-1 gene expression under normal oxygen environment [53].

The level of HIF-1α is a key factor for the angiogenesis and tissue reconstruction in the body [54]. Inhibition of the expression of HIF-1α in rat pulmonary vessels can effectively reduce pulmonary hypertension and pulmonary vascular remodeling, while in HIF-1α knocked out mouse pulmonary artery smooth muscle cells, hypoxic stimulation did not cause pulmonary hypertension [55].

HIF-1 is widely expressed in neurons, glial cells and ependymal cells in the central nervous system under hypoxia conditions [56]. The expression of HIF-1 is enhanced after epilepsy, and HIF-1 promotes the proliferation and differentiation of neural stem cells in the hippocampus. Moreover, HIF-1 mediates hippocampal cell apoptosis and neuronal loss in acute epilepsy through the Notch signaling pathway [57]. It has been demonstrated that the expression of HIF-1 significantly reduces in epileptic mice after treatment with DAPT (an inhibitor of the Notch pathway), while HIF-1 level significantly increases in untreated mice [58].

Notably, HIF-1 is also highly expressed in a variety of tumor cells. Tumors, like normal tissues, require a constant supply of oxygen and nutrients. However, with the continuous expansion of tumors, the oxygen in the host blood vessels is insufficient to meet the needs of tumor growth. Therefore, malignant microenvironment mainly developed under hypoxia conditions is formed inside the tumors. HIFs, as the most important transcription factor, can activate the expression of many genes to protect tumor cells from encroaching [59-62], including (1) activation of angiogenic genes to increase blood flow in hypoxic areas, (2) conversion of energy metabolism into glycolytic pathways that require less oxygen, and (3) disruption of cell cycle. Meanwhile, HIFs can also up-regulate the expressions of various target genes and protein biosynthesis, such as erythropoiesis, glycolysis, EMT, metastasis, angiogenesis and treatment resistance, which not only increases the survival of tumors, but also increases their invasiveness and metastasis. Hence, inhibiting the expression of HIF-1α and its related factors is of great significance for cancer treatment, prognosis assessment and targeted therapy [63].

In summary, HIF-1 participates in important biological processes associated with the survival and development by regulating the transcriptional activation of numerous genes, and is closely related to many human diseases, such as cancer, retinal development, alzheimer's disease, stroke and diabetic foot ulcer (Fig. 4).

Natural Products as Direct Modulators of HIF-1

Protein-protein interaction (PPI) is crucial in regulating physiological processes and closely related to the pathogenesis of diseases [64]. Therefore, the development of PPI inhibitors has attracted increasing attention. Currently, some PPI inhibitors have been assessed in clinical trials [65]. Natural products have unique frameworks, functional groups and excellent biological activities. With the development of modern chemistry and bioinformatics tools, more and more lead compounds have been discovered [66]. Here, we then summarize the PPI inhibitors derived from natural products that can directly act on HIF-1 protein to illustrate the research progress on the development of PPI inhibitors of HIF-1 in recent years (Fig. 5).

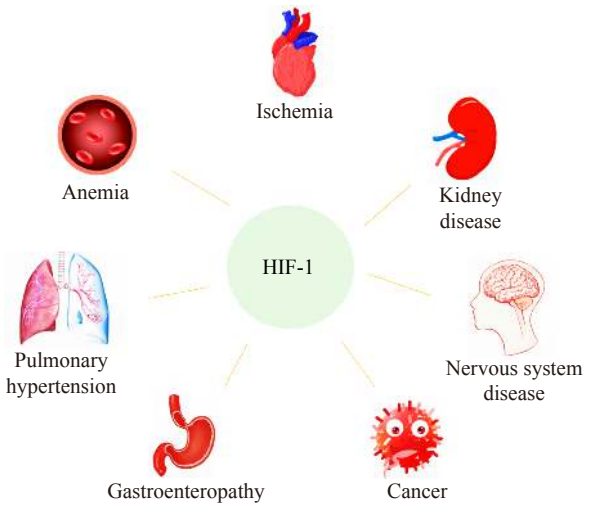

Fig. 4 The roles of HIF-1 in human diseases. Activation of HIF-1 or increasing the expression of HIF-1 facilitates the treatment of HIF-related diseases (anemia, ischemia, wound healing, gastrointestinal ulcer, and stroke, etc.), while inhibition of the activity of HIF-1 can help to treat cancer, and pulmonary hypertension, etc.

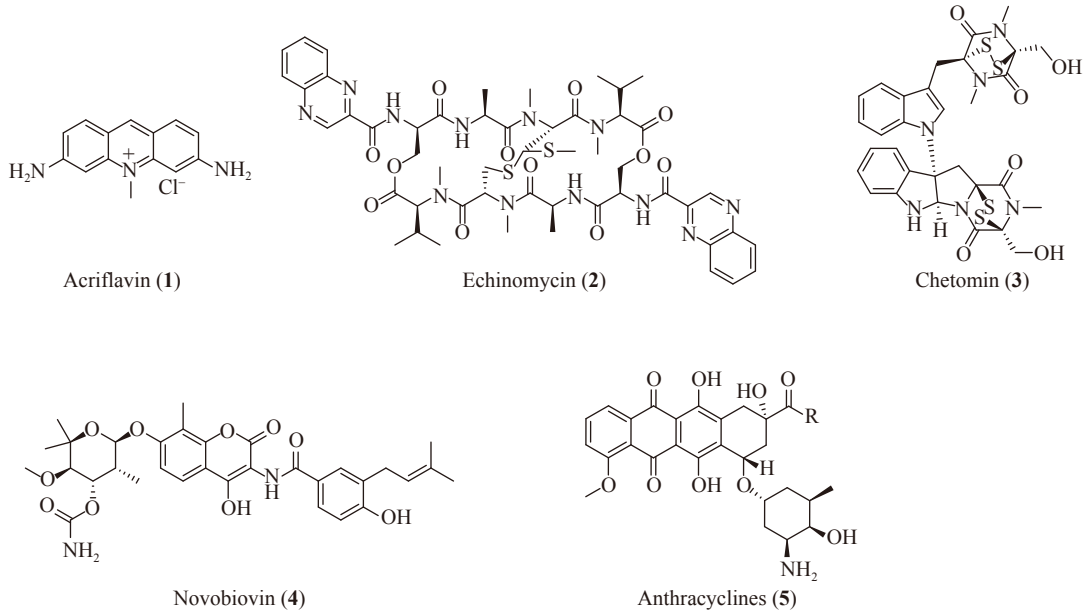

Fig. 5 Chemical structures of compounds that directly bind to HIF-1. Acriflavin is extracted from coal tar. Echinomycin is separated from the fermentation broth of *Streptomyces echinatus*. Chetomin is an antibiotic metabolite of chaetomium cochliodes. Novobiocin is a representative drug of coumarin antibiotics. Anthracycline is derived from *Streptomyces peucetius* var. *caesius*

Acriflavin (**1**) prevents the dimerization of HIF-1 through binding to the PAS-B domain, which resulted in remarkable decreases in the HRE-directed activity, and can be a potential compound for the treatment of cancers caused by the overexpression of HIF-1α or HIF-2α [67]. Echinomycin (**2**) is a natural cyclic peptide that can specifically occupy the binding site of HIF-1 and DNA, thereby down-regulating HIF-1-induced signaling pathways [68]. Chetomin (**3**) can bind to the CH1 domain of p300 and block its binding with HIF-1α, thus decreasing gene transactivation induced by activated HRE [69]. It also displays anti-cancer activity in human myeloma cell lines, suggesting that chetomin may have clinical application value for the treatment of multiple myeloma, especially in patients with abnormal expression of p300/HIF-1α [70]. Similarly, novobiocin (**4**) can also block the binding of HIF-1 to p300 [71]. It can effectively inhibit the proliferation of various tumor cells, and be used in combination with anti-tumor drugs to overcome the resistance of anti-tumor drugs. Anthracycline (**5**), a well-known chemotherapeutic agent, interrupts HIF-1α binding to DNA and weakens the transcriptional activity of downstream genes [72].

Conclusions

Natural products have unique and novel structures and are the main source of drugs or important lead compounds for the treatment of major diseases [73-75]. Although many small-molecule inhibitors of HIF-1 have been reported, there are only a few inhibitors derived from natural products which can directly target and bind to the HIF-1 protein. Notably, HIF-1 is a major transcriptional activator for promoting angiogenesis, but its natural product-derived activators have not been found.

Moreover, recent studies have indicated that HIF-1 is involved in regulating epigenetic, non-coding RNA, circadian clock and other biological processes [9]. These processes are related to the pathogenesis of various tumors, including liver, colorectal, breast, blood and lung cancers [76]. For example, HIF-1 is involved in regulating the proliferation, cell cycle and apoptosis of colorectal cancer cells by inducing KDM4B [77]. miR-210 or lncRNA stabilizes HIF-1 in various ways to promote tumor cell migration and invasion [78]. The basic components of the circadian clock and oxygen homeostasis are the members of the PAS protein family (PER and CLOCK) and HIF-1α [9]. The circadian clock pathway involves many genes that disrupt the responses to hypoxia under disease and stress conditions, thereby affecting physiological processes and disease progression [79].

In summary, HIF-1 can interfere with the expression of more than 200 genes, thereby regulating growth factor synthesis, cell proliferation and apoptosis, energy metabolism, inflammation, and tumor radiochemotherapy sensitivity. However, no natural product-derived inhibitors of HIF-1α have been approved for clinical use. In addition, some approved drugs that indirectly affect the HIF-1 pathway can be used as adjuvant therapy for certain diseases. In view of the important role of natural products, especially for the treatment of COVID-19, there is an urgent need to develop more natural HIF-1 regulators.

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